CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER***:***

201635Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

STATEMENT PURSUANT TO SECTION 505(b)(2)(B)
of the Federal Food, Drug and Cosmetic Act

Re: U.S. Patent Nos. 5,998,380, 6,503,884, 7,018,983, and 7,498,311

In accordance with the Federal Food, Drug, and Cosmetic Act, a statement pursuant to section 505(b)(2)(B) of the Federal Food, Drug, and Cosmetic Act is hereby provided for our 505(b)(2) New Drug Application #201635 for our Topiramate Extended-Release Capsules, 25mg, 50mg, 100mg, 200mg.

U.S. Patent Nos. 5,998,380 and 6,503,884 claim a method of use, use code U-598, "PROPHYLACTIC TREATMENT OF MIGRAINE" for which Supernus Pharmaceuticals, Inc. is not seeking approval in this application.

U.S. Patent No. 7,018,983 claims a method of use, use code U-723, "PROPHYLACTIC TREATMENT OF MIGRAINE" for which Supernus Pharmaceuticals, Inc. is not seeking approval in this application.

U.S. Patent No. 7,498,311 claims a method of use, use code U-955, "PROPHYLACTIC TREATMENT OF MIGRAINE" for which Supernus Pharmaceuticals, Inc. is not seeking approval in this application.

Padmanabh P. Bhatt, Ph.D.
Vice President, Pharmaceutical Sciences
Supernus Pharmaceuticals, Inc.

July 11, 2011
Date

PATENT CERTIFICATION

Paragraph IV Certification

Re: U.S. Patent Nos. 7,125,560

In accordance with the Federal Food, Drug, and Cosmetic Act, Patent Certification is hereby provided for our 505(b)(2) New Drug Application #201635 for our product Topiramate Extended-Release Capsules, 25mg, 50mg, 100mg, 200mg.

Supernus Pharmaceuticals, Inc. hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. 7,125,560 assigned to Ortho-McNeil Pharmaceuticals, Inc. and listed in the FDA's Orange Book under Ortho-McNeil Janssen, NDA 20-844 for TOPAMAX®, expiring on March 1, 2019, is invalid, unenforceable and/or will not be infringed by the manufacture, use or sale of Topiramate Extended-Release Capsules for which this 505(b)(2) NDA is submitted. Supernus Pharmaceuticals, Inc. acknowledges that U.S. Patent No. 7,125,560 has been extended by pediatric exclusivity to September 1, 2019.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Federal Food, Drug and Cosmetic Act and 21 CFR § 314.52(a), and 21 CFR § 314.52(c), Supernus Pharmaceuticals, Inc. hereby states that Supernus Pharmaceuticals, Inc. will give notice required by the Federal Food, Drug and Cosmetic Act and 21 CFR § 314.52(a) to Ortho-McNeil Janssen, the holder of the approved new drug application for TOPAMAX® (Topiramate) Capsules, NDA 20-844 and the owner (assignee) of US Patent No. 7,125,560, Ortho-McNeil Pharmaceuticals, Inc. This notice to Ortho-McNeil Janssen and Ortho-McNeil Pharmaceuticals, which will be sent by certified mail, return receipt requested, or by overnight mail with approval from FDA shall meet the requirements of 21 CFR § 314.52(a) and 314.52(c).

Concurrently with sending the notice to Ortho-McNeil Janssen and Ortho-McNeil Pharmaceuticals, Supernus Pharmaceuticals, Inc. as required by 21 CFR § 314.52(b), will amend its 505(b)(2) NDA to include a certification that the notice has been provided to each person identified under 21 CFR §314.52 (a) and that the notice met the content requirements of 21 CFR § 314.52(c).

Padmanabh P. Bhatt, Ph.D.
Vice President, Pharmaceutical Sciences
Supernus Pharmaceuticals, Inc.

July 11, 2011
Date

STATEMENT PURSUANT TO SECTION 505(b)(2)(B)
of the Federal Food, Drug and Cosmetic Act

Re: U.S. Patent Nos. 5,998,380, 6,503,884, 7,018,983, and 7,498,311

In accordance with the Federal Food, Drug, and Cosmetic Act, a statement pursuant to section 505(b)(2)(B) of the Federal Food, Drug, and Cosmetic Act is hereby provided for our 505(b)(2) New Drug Application #201635 for our Topiramate Extended-Release Capsules, 25mg, 50mg, 100mg, 200mg.

U.S. Patent Nos. 5,998,380 and 6,503,884 claim a method of use, use code U-598, "PROPHYLACTIC TREATMENT OF MIGRAINE" for which Supernus Pharmaceuticals, Inc. is not seeking approval in this application.

U.S. Patent No. 7,018,983 claims a method of use, use code U-723, "PROPHYLACTIC TREATMENT OF MIGRAINE" for which Supernus Pharmaceuticals, Inc. is not seeking approval in this application.

U.S. Patent No. 7,498,311 claims a method of use, use code U-955, "PROPHYLACTIC TREATMENT OF MIGRAINE" for which Supernus Pharmaceuticals, Inc. is not seeking approval in this application.

Nov 30, 2010

Padmanabh P. Bhatt, Ph.D.
Vice President, Pharmaceutical Sciences
Supernus Pharmaceuticals, Inc.

Date

PATENT CERTIFICATION

Paragraph IV Certification

Re: U.S. Patent Nos. 7,125,560

In accordance with the Federal Food, Drug, and Cosmetic Act, Patent Certification is hereby provided for our 505(b)(2) New Drug Application #210635 for our product Topiramate Extended-Release Capsules, 25mg, 50mg, 100mg, 200mg.

Supernus Pharmaceuticals, Inc. hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. 7,125,560 assigned to Ortho-McNeil Pharmaceuticals, Inc. and listed in the FDA's Orange Book under Ortho-McNeil Janssen, NDA 20-844 for TOPAMAX®, expiring on March 1, 2019, is invalid, unenforceable and/or will not be infringed by the manufacture, use or sale of Topiramate Extended-Release Capsules for which this 505(b)(2) NDA is submitted. Supernus Pharmaceuticals, Inc. acknowledges that U.S. Patent No. 7,125,560 has been extended by pediatric exclusivity to September 1, 2019.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Federal Food, Drug and Cosmetic Act and 21 CFR § 314.52(a), and 21 CFR § 314.52(c), Supernus Pharmaceuticals, Inc. hereby states that Supernus Pharmaceuticals, Inc. will give notice required by the Federal Food, Drug and Cosmetic Act and 21 CFR § 314.52(a) to Ortho-McNeil Janssen, the holder of the approved new drug application for TOPAMAX® (Topiramate) Capsules, NDA 20-844 and the owner (assignee) of US Patent No. 7,125,560, Ortho-McNeil Pharmaceuticals, Inc. This notice to Ortho-McNeil Janssen and Ortho-McNeil Pharmaceuticals, which will be sent by certified mail, return receipt requested, or by overnight mail with approval from FDA shall meet the requirements of 21 CFR § 314.52(a) and 314.52(c).

Concurrently with sending the notice to Ortho-McNeil Janssen and Ortho-McNeil Pharmaceuticals, Supernus Pharmaceuticals, Inc. as required by 21 CFR § 314.52(b), will amend its 505(b)(2) NDA to include a certification that the notice has been provided to each person identified under 21 CFR §314.52 (a) and that the notice met the content requirements of 21 CFR § 314.52(c).

Padmanabh P. Bhatt, Ph.D.
Vice President, Pharmaceutical Sciences
Supernus Pharmaceuticals, Inc.

Nov 30, 2010
Date

EXCLUSIVITY SUMMARY

NDA # 201635 SUPPL # HFD #

Trade Name Trokendi XR

Generic Name topiramate extended release capsules

Applicant Name Supernus Pharmaceuticals, Inc.

Approval Date, If Known August 16, 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The applicant sought approval by applying a NOVEL bioequivalence (BE)-based method in pharmacokinetic (PK) studies without conducting a clinical efficacy trial. The studies conducted, 538P103 and 538P108, were reviewed by the Clinical team for adverse events, not efficacy. Both studies were also reviewed by Clinical Pharmacology for pharmacokinetic and pharmacodynamics (PD) effects. Studies 538P103 and 538P108 were relative bioavailability studies and were not adequately designed efficacy studies (open label conversion studies).

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

n/a

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?
3 years

The firm also submitted a justification for 3-year Hatch-Waxman exclusivity. The request and justification were reviewed by the CDER Exclusivity Board on November 8, 2013, who recommended that the request be denied. The firm was notified via a December 4, 2013 letter that the NDA was not eligible for 3 years of exclusivity.

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☒ NO ☐

If the answer to the above question is YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No. The reference listed drug, Topamax® (NDA 20844 and 20505) was granted pediatric exclusivity, which expired on June 22, 2013. Topamax® also received new patient population exclusivity, which expires on September 1, 2019.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this

particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20844 Topamax® (topiramate) Sprinkle Capsules

NDA# 20505 Topamax® (topiramate) Tablets

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application

and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Taura Holmes, PharmD

Title: Regulatory Project Manager
Date: December 4, 2013

Name of Office/Division Director signing form: Eric Bastings, MD
Title: Acting Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TAURA N HOLMES
12/06/2013

ERIC P BASTINGS
12/08/2013

3 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

1.3.3 Debarment Certification

Supernus Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Tami T. Martin
Signature/Title

28 June 2011
Date

Tami T. Martin, RN, Esq.
Vice President, Regulatory Affairs
Supernus Pharmaceuticals, Inc.
tmartin@supernus.com

1.3.3 Debarment Certification

Supernus Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Tami T Martin
Signature/Title

Nov 3, 2010
Date

Tami T. Martin, RN, Esq.
Vice President, Regulatory Affairs
Supernus Pharmaceuticals, Inc.
tmartin@supernus.com

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 201635 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Trokendi XR Established/Proper Name: topiramate extended-release Dosage Form: capsules		Applicant: Supernus Pharmaceuticals Agent for Applicant (if applicable): Tami Martin
RPM: Taura Holmes, PharmD		Division: Division of Neurology Products

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Topamax (topiramate) Tablets (NDA 20505)
Topamax (topiramate) Sprinkle Capsules (NDA 20844)

Provide a brief explanation of how this product is different from the listed drug.

This application provided for a new extended-release dosage form. The RLDs are immediate-release products.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☒ This application relies on (explain) an already approved IR product

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☑ No changes ☐ Updated Date of check: 08/16/13

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is **August 18, 2013**	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None TA (June 25, 2012) TA (June 7, 2013) RTF (March 14, 2011)

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists documents to be included in the Action Package.

[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No
• Press Office notified of action (by OEP)	☐ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☒ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☒ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☒ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☒ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☒ No

CONTENTS OF ACTION PACKAGE

1. ❖ Copy of this Action Package Checklist[4]	
Officer/Employee List	
2. ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☐ Included
Documentation of consent/non-consent by officers/employees	☐ Included
Action Letters	
3. ❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s)
Labeling	
4. ❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	

[4] Fill in blanks with dates of reviews, letters, etc.

5. ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
6. ❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	
7. ❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	
8. ❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☐ DMEPA ☐ DMPP/PLT (DRISK) ☐ ODPD (DDMAC) ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
9. ❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2)
10. ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☐ Not a (b)(2)
11. ❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
13. ❖ Pediatrics *(approvals only)* • Date reviewed by PeRC May 23, 2012 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☐ Included
14. ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

15. ❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	
❖ Internal memoranda, telecons, etc.	
16. ❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☐ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
17. Division Director Summary Review *(indicate date for each review)*	☐ None
18. Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None
19. PMR/PMC Development Templates *(indicate total number)*	☐ None
Clinical Information[6]	
20. ❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	
• Clinical review(s) *(indicate date for each review)*	
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
21. ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested

[6] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None
22. Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None
Nonclinical ☐ None	
23. ❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
24. ❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

Supernus Pharmaceuticals, Inc.
1550 East Gude Drive
Rockville, MD 20850
Tel (301) 838-2500
Fax (301) 424-1385

Supernus Pharmaceuticals

August 5, 2013

Russell G. Katz, M.D., Director
Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research
Office of New Drugs
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA #:	**201635**
Sponsor:	**Supernus Pharmaceuticals, Inc.**
Product:	**SPN-538, Topiramate Extended-Release Capsules**
Sequence #:	**S0038**
Submission Type:	**Response to Request for Information** **Pediatric Plan** **Post-Marketing Requirements**

Dear Dr. Katz:

This submission pertains to NDA 201635 which received Tentative Approval on June 7, 2013.

Response to Request for Information

As requested Supernus is providing an amended Pediatric Plan which follows recommendations received from the Agency on August 1, 2013.

Supernus acknowledges waiver and deferral recommendations made in this communication. Further, Supernus Pharmaceuticals, Inc. Accepts the FDA's comments pertaining to post-marketing commitments, and commits to making best, timely efforts to create a suitable pediatric formulation for young children as described in the Pediatric Plan. Assuming a suitable formulation can be created, Supernus further commits to the conduct of PK and clinical work utilizing this formulation as outlined in the Pediatric Plan.

This official submission is being provided in electronic Common Technical Document (eCTD) format. This submission contains materials for one module:

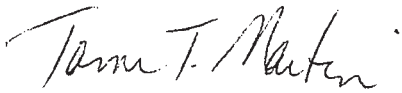
Module 1: Administrative Information including

Cover letter
Form FDA 356h
1.9.6 Pediatric Plan

The entire content of this submission is provided on a CD-ROM following ICH eCTD specifications. Signed forms are also provided on paper. One copy of the electronic submission is being provided. This application has been verified and confirmed to be virus-free.

Please contact the undersigned directly with any questions or comments about this submission.

Sincerely,



Tami T. Martin, RN, Esq.
Vice President, Regulatory Affairs
Supernus Pharmaceuticals, Inc.
Phone: 301-838-2607
FAX: 301-424-1364
Email: tmartin@supernus.com

Pediatric Plan

Table of Contents

1.0 Background

1.1 505(b)(2) NDA

As a 505(b)(2) New Drug Application, Supernus is relying on pediatric work conducted by the makers of Topamax®(immediate-release topiramate, NDA # 020505) to support NDA 201635. Topamax is indicated for epilepsy monotherapy in children 2 to <10 years of age, dosage based on weight, and, for children ≥10, titrated to a recommended dosage of 400mg/day in two divided doses. For epilepsy adjunctive therapy, pediatric patients with partial onset seizures, primary generalized tonic-clonic seizures or Lennox-Gastaut syndrome are to be titrated to a dose guided by clinical outcome. Although titration instructions are provided, the adjunctive therapy indicatior (b) (4)

(b) (4)

1.2 FDA meetings/discussion/guidance

On August 1, 2013, Supernus received an e mail communication with final recommendations from the Agency concerning continuing expectations, granting of waiver in limited pediatric populations, and postmarketing requirements in pediatric populations. This revised Pediatric Plan accepts all FDA recommendations for additional postmarketing evaluations and presents timelines for their completion.

1.3 Company Work to Date

(b) (4)

(b) (4)

2.0 Pediatric plan for children ages 6 to 17 years

FDA recommendation: Once approved, we will consider your product to be appropriately labeled for pediatric patients 6 to 17 years. Therefore, no additional studies will be required for this age group.

Supernus Response: Supernus will not plan on conducting additional work in this age group.

3.0 Pediatric Waiver

FDA recommendations: We will waive pediatric studies for the following indications and age groups because studies are impracticable because of the small number of patients and the difficulty diagnosing such age groups:

a. Adjunctive therapy in partial onset seizures (POS): Birth to < 1 month

b. Initial monotherapy in POS and primary generalized tonic-clonic (PGTC) seizures, Adjunctive therapy in Primary Generalize Tonic Seizures, and Adjunctive therapy in Lennox-Gastaut Syndrome: Birth to < 2 years.

Supernus Response: Supernus accepts these waiver recommendations and will not conduct additional work in these specific age groups/populations.

4.0 Pediatric Deferrals

FDA recommendations: We will defer pediatric studies for the following indications and age groups:

a. Adjunctive therapy in partial onset seizures (POS): 1 month to < 6 years

b. Initial monotherapy in POS and primary generalized tonic-clonic (PGTC) seizures, Adjunctive therapy in Primary Generalize Tonic Seizures, and Adjunctive therapy in Lennox-Gastaut Syndrome: 2 years to < 6 years

Supernus response: Supernus accepts these deferral recommendations.

5.0 Postmarketing Commitments for Pediatric Work

FDA Requirements: These studies will be required in accordance with section 505B(a) of the Federal Food, Drug, and Cosmetic Act and will be required post-marketing studies. The status of these post-marketing studies should be reported annually in accordance with 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act.

PMR 1 Develop an age appropriate formulation of Trokendi XR (topiramate) extended-release capsules that can be used in children 1 month to less than 6 years old.

Final Protocol Submission: MM/YY

Study/Trial Completion: MM/YY

Final Report Submission: MM/YY

PMR 2 A study to evaluate the pharmacokinetics (PK) and tolerability of an age-appropriate formulation of Trokendi XR (topiramate) extended-release capsules, developed in PMR 1, in children ages 2 years to less than 6 years with partial onset seizures (POS), primary generalized tonic-clonic (PGTC) seizures, and/or Lennox-Gastaut syndrome (LGS), and evaluating bioavailability after administration once daily relative to bioavailability of the reference listed drug, Topamax, given twice daily.

Final Protocol Submission: MM/YY

Study/Trial Completion: MM/YY

Final Report Submission: MM/YY

PMR 3 A study to evaluate the PK and tolerability of an age-appropriate formulation of Trokendi XR (topiramate) extended-release capsules, developed in PMR 1, as adjunctive therapy in children ages 1 month to less than 2 years with partial onset seizures (POS).

Final Protocol Submission: MM/YY

Study/Trial Completion: MM/YY

Final Report Submission: MM/YY

PMR 4 An adequately controlled study to assess the efficacy and safety of an age-appropriate formulation of Trokendi XR (topiramate) extended-release capsules, developed in PMR 1, as adjunctive therapy in children ages 1 month to less than 2 years with partial onset seizures (POS).

Final Protocol Submission: MM/YY

Study/Trial Completion: MM/YY

Final Report Submission: MM/YY

Supernus Response:

Supernus commits to the conduct of these activities as follows:

5.1Postmarketing Requirement #1: Formulation Development

Supernus will make best efforts to develop an age appropriate formulation of Trokendi XR (topiramate) extended-release capsules that can be used in children 1 month to less than 6 years old. (b) (4)

(b) (4)

5.2 Postmarketing Requirement #2: PK /Tolerability study ages 2 to less than 6 years of age

Supernus would conduct a study to evaluate the pharmacokinetics (PK) and tolerability of an age-appropriate formulation of Trokendi XR (topiramate) extended-release capsules, (as developed in PMR #1), in children ages 2 years to less than 6 years with partial onset seizures (POS), primary generalized tonic-clonic (PGTC) seizures, and/or Lennox-Gastaut syndrome (LGS), and evaluating bioavailability after administration once daily relative to bioavailability of thereference listed drug, Topamax, given twice daily. (b) (4)

(b) (4)

Final Protocol Submission: November 2015

Study/Trial Completion: November 2018

Final Report Submission: May 2019

5.3 Postmarketing Commitment #3: PK/Tolerability study in children ages 1 month to less than 2 years

Supernus commits to conduct study to evaluate the PK and tolerability of an age-appropriate formulation of Trokendi XR (topiramate) extended-release capsules, (as developed in PMR #1), as adjunctive therapy in children ages 1 month to less than 2 years with partial onset seizures

(POS). (b) (4)

(b) (4)

Final Protocol Submission: February 2016

Study/Trial Completion: February 2019

Final Report Submission: August 2019

5.4 Postmarketing Requirement #4: Clinical safety and efficacy in children ages 1 month to less than 2 years

Supernus commits to the conduct of an adequately controlled study to assess the efficacy and safety of an age-appropriate formulation of Trokendi XR (topiramate) extended-release capsules, (as developed in PMR #1), as adjunctive therapy in children ages 1 month to less than 2 years with partial onset seizures (POS). (b) (4)

(b) (4)

Final Protocol Submission: November 2019

Study/Trial Completion: November 2024

Final Report Submission: August 2025

6.0 References

Guidance for Industry: Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications (April 2003)

Food and Drug Administration. Advisory Committee for Pharmaceutical Science and Clinical Pharmacology Meeting, March 14, 2012, National Harbor, MD: Committee Presentation by S. Huang:
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM298465.pdf.

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

Date: July 29, 2013

To: File for NDA 201635

From: Melinda McLawhorn, PharmD, BCPS

Subject: **Informal MO consult from DNP on advisory (attached)**

Reference ID: 3424690

McLawhorn, Melinda

From: Hershkowitz, Norman
Sent: Wednesday, July 24, 2013 3:59 PM
To: McLawhorn, Melinda
Subject: RE: Update from DNP regarding Trokendi XR

yes

From: McLawhorn, Melinda
Sent: Wednesday, July 24, 2013 2:41 PM
To: Hershkowitz, Norman
Cc: Fienkeng, Mathilda; Rusinowitz, Martin
Subject: RE: Update from DNP regarding Trokendi XR

Thanks for the follow-up, Dr Hershkowitz. Just to clarify, the bioequilvance approval would constitute substantial evidence to support "(b) (4) conversion" claims with Trokendi XR. Is this correct?

M^2

From: Hershkowitz, Norman
Sent: Wednesday, July 24, 2013 12:50 PM
To: McLawhorn, Melinda
Cc: Fienkeng, Mathilda; Rusinowitz, Martin
Subject: RE: Update from DNP regarding Trokendi XR

Hi Melinda,

Yes, we met. As we state in the labnbel that both drugs are "bioequivalent," we decidied not to put any caveat in about switching. So a (b) (4) conversion would be assumed.

Norm

From: McLawhorn, Melinda
Sent: Wednesday, July 24, 2013 9:54 AM
To: Hershkowitz, Norman
Cc: Fienkeng, Mathilda
Subject: FW: Update from DNP regarding Trokendi XR

Hi Dr Hershkowitz,

Dr Rusinowitz mentioned that you were scheduled to meet yesterday to discuss the Trokendi XR core launch sales aid concerning claims about (b) (4) conversion (see below). I understand he is out of the office and was wondering if you might be able to provide direction to me regarding your impression of the use of such claims in promotion. Many thanks!

Melinda W McLawhorn, PharmD, BCPS
LCDR US Public Health Service
Regulatory Review Officer
Office of Prescription Drug Promotion
10903 New Hampshire Ave, Bld 51, room 3254
Silver Spring MD 20993
Phone: 301-796-7559
Fax: 301-847-8444
Email: Melinda.mclawhorn@fda.hhs.gov

From: Rusinowitz, Martin
Sent: Wednesday, July 17, 2013 2:52 PM
To: McLawhorn, Melinda
Subject: RE: Voice Message from McLawhorn, Melinda (83017967559)

Hi Melinda,

There's no update on this issue other than to let you know we have a meeting scheduled to discuss this next Tuesday morning with Dr. Bastings (Acting Director of DNP) and Dr. Hershkowitz. I will be out on annual leave all of next week, but I'll ask Norm to let you know the results. Sorry for the delay, that was the earliest we could get this meeting on the calendar.

Martin

Martin S. Rusinowitz, M.D.
Medical Review Officer
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone 301-796-0158 Fax 301-796-9842
Email Martin.Rusinowitz@fda.hhs.gov

From: McLawhorn, Melinda
Sent: Wednesday, July 17, 2013 11:53 AM
To: Rusinowitz, Martin
Subject: Voice Message from McLawhorn, Melinda (83017967559)

<< File: VoiceMessage.wav >>

McLawhorn, Melinda

From: Rusinowitz, Martin
Sent: Friday, June 28, 2013 9:51 AM
To: McLawhorn, Melinda
Subject: RE: promotional claims regarding converting from IR topirimate to XR topiramate

Hi Melinda,

Sorry for taking so long to get back to you. I've been in and out much of the week and my lack of organization skills are way too obvious.

This issue has come up often and, as you indicate, some labels have dealt with the conversion while this one has not. In general, I don't think we ever really know the best way to convert from an immediate release product to a long acting one. The claims of (b) (4) conversion", "No washout", and "No titration." would therefore be true, but no different than that for any product conversion. The ad makes it sound as if these properties are special or unique and they are not. In that regard it's deceptive.

I want to run this by my team leader, Norm Hershkowitz, and I promise I'll get back to you with a more definitive answer on Mon. or Tues. of next week.

Thanks, have a great weekend.

Martin

Martin S. Rusinowitz, M.D.
Medical Review Officer
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone 301-796-0158 Fax 301-796-9842
Email Martin.Rusinowitz@fda.hhs.gov

From: McLawhorn, Melinda
Sent: Friday, June 21, 2013 1:57 PM
To: Rusinowitz, Martin
Subject: promotional claims regarding converting from IR topirimate to XR topiramate

Hi Dry Rusinowitz,
Hope this message finds you well and enjoying the summer (which is going by way too fast in my opinion)! I am reviewing proposed launch materials for Trokendi XR and have a question regarding conversion from IR topiramate to Trokendi XR. I was wondering if I could informally ask for your perspective on 'conversion claims' with Trokendi XR?

The proposed visual aid include claims like (b) (4) **conversion", "No washout"**, and **"No titration."** I noted that the PI doesn't discuss conversion. However, we have placed information about conversion in other labels (i.e. Lamictal XR: The initial dose of LAMICTAL XR should match the total daily dose of the immediate-release lamotrigine. Patients should be closely monitored for seizure control after conversion).

Do you recall if there were discussions during labeling meetings about including language about conversion from IR topiramate? Do you have any concerns about a direct conversion from topiramate even though the drugs are bioequivalent? Should they include a cautionary statement like "**Patients** should be closely monitored for seizure control after **conversion**" even though we **don't** have this info in the PI?

I've attached a copy for your reference. Thanks in advance for your insight.

Melinda W McLawhorn, PharmD, BCPS
LCDR US Public Health Service
Regulatory Review Officer
Office of Prescription Drug Promotion
10903 New Hampshire Ave, Bld 51, room 3254
Silver Spring MD 20993
Phone: 301-796-7559
Fax: 301-847-8444
Email: Melinda.mclawhorn@fda.hhs.gov

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/s/

MELINDA W MCLAWHORN
07/29/2013

Supernus Pharmaceuticals, Inc.
1550 East Gude Drive
Rockville, MD 20850
Tel (301) 838-2500
Fax (301) 424-1385

Supernus® Pharmaceuticals

June 20, 2013

Russell G. Katz, M.D., Director
Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research
Office of New Drugs
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA #:	**201635**
Sponsor:	**Supernus Pharmaceuticals, Inc.**
Product:	**SPN-538, Topiramate Extended-Release Capsules**
Sequence #:	**S0037**
Submission Type:	**30-count Blister Commercial Container Labels - 200mg**

Dear Dr. Katz:

This submission pertains to NDA 201635 which received Tentative Approval on June 25, 2012.

Response to Request for Information

The 200 mg 30-count blister commercial label that was provided in Sequence 0036 was incorrect; color shading on the back of the card was missing from two blister openings. The corrected 30-count blister commercial label for the 200 mg dosage strength is enclosed.

This official submission is being provided in electronic Common Technical Document (eCTD) format. This submission contains materials for one module:

Module 1: Administrative Information, including
Cover letter
Form FDA 356h
1.14.1.1 30-count Blister Label - 200 mg

The entire content of this submission is provided on a CD-ROM following ICH eCTD specifications. Signed forms are also provided on paper. One copy of the electronic submission is being provided. This application has been verified and confirmed to be virus-free.

Please contact the undersigned directly with any questions or comments about this submission.

Sincerely,

for

Tami T. Martin, RN, Esq.
Vice President, Regulatory Affairs
Supernus Pharmaceuticals, Inc.
Phone: 301-838-2607
FAX: 301-424-1364
Email: tmartin@supernus.com

3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

FOOD AND DRUG ADMINISTRATION
Office of Prescription Drug Promotion

EVIDENCE REVIEW CONSULT RESPONSE

Date: June 18, 2013

To: Melinda McLawhorn

From: Elaine Hu Cunningham

Subject:

NDA#:	
Proprietary Name:	Trokendi XR
Generic Name:	topiramate extended-release capsules for oral use
Sponsor:	Supernus Pharmaceuticals, Inc.

DARRTS MA#: 3

DARRTS SD#: 40

Background:

This consult provides regulatory advice pertaining to claims in a proposed professional sales aid for Trokendi XR (topiramate extended-release capsules for oral use) that was submitted to OPDP for core launch advisory comments.

Trokendi XR is indicated for the following:

- **Partial onset seizure and generalized tonic-clonic seizures:** Initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures and adjunctive therapy in patients 6 years of age and older with partial onset or primary generalized tonic-clonic seizures trials. Safety and effectiveness in patients who were converted to monotherapy from a previous regimen of other anticonvulsant drugs have not been established in controlled trials.

- **Lennox-Gastaut Syndrome:** Adjunctive therapy in patients 6 years of age and older with seizures associated with Lennox-Gastaut syndrome.

Topamax (topiramate tablets for oral use and sprinkle capsules for oral use) are indicated for:

- **Monotherapy epilepsy:** initial monotherapy in patients ≥2 years of age with partial onset or primary generalized tonic-clonic seizures

- **Adjunctive therapy epilepsy:** adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients ≥ 2 years of age with seizures associated with Lennox-Gastaut syndrome

- **Migraine:** treatment for adults for prophylaxis of migraine headache

Topamax is also available as a generic product through several different manufacturers.

Review and Summary:

The proposed professional sales aid for Trokendi XR includes the following claims (bolded emphasis in original; underlined emphasis added):

(b) (4)

[redacted]

(b) (4) It is recommended that the proposed claims be revised or deleted.

[redacted]

(b) (4)

SIGNED:

Thank you for this opportunity to provide comments! If you have any questions, please feel free to contact me at 6-0596 or Elaine.Cunningham@FDA.HHS.GOV.

Drafted: Cunningham/06-18-2013

Consult: Betts (social science)/06-18-2013

Finalized: Cunningham/06-18-13

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/s/

ELAINE H CUNNINGHAM
06/20/2013

Supernus Pharmaceuticals, Inc.
1550 East Gude Drive
Rockville, MD 20850
Tel (301) 838-2500
Fax (301) 424-1385

June 17, 2013

Russell G. Katz, M.D., Director
Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research
Office of New Drugs
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA #:	**201635**
Sponsor:	**Supernus Pharmaceuticals, Inc.**
Product:	**SPN-538, Topiramate Extended-Release Capsules**
Sequence #:	**S0036**
Submission Type:	**Response to Request for Information** **Draft Labelling Text** **30-count Blister Commercial Container labels** **100-count Commercial Bottle labels** [redacted] (b) (4) **Medication Guide**

Dear Dr. Katz:

This submission pertains to NDA 201635 which received Tentative Approval on June 7, 2013.

Response to Request for Information

As requested Supernus is providing the current versions of:

- Draft labelling text
- 30-count commercial blister packaging container/closure labels
- 100-count commercial bottle packaging container labels
- [redacted] (b) (4)
  - Medication Guide, track change version and clean version

Draft labelling text is unchanged from Sequence 0033, blister packaging configurations are unchanged from Sequence 0034, and bottle labels are unchanged from Sequence 0031; meaning there is no change in any of those items following the June 7, 2013 Tentative Approval.

The Medication Guide has been updated to add current issue dates, remove the header, and add pagination. The content is otherwise unchanged from that agreed upon in June, 2012, and presented in the Tentative Approval at that time. These minor updates are captured in a track change version included in this submission. A clean version of the Medication Guide is also provided.

This official submission is being provided in electronic Common Technical Document (eCTD) format. This submission contains materials for one module:

Module 1: Administrative Information including

Cover letter	
Form FDA 356h	
1.14.1.1	(b) (4)
1.14.1.1	
1.14.1.1	
1.14.1.1	
1.14.1.1	30-count Blister Label—25mg
1.14.1.1	30-count Blister Label—50mg
1.14.1.1	30-count Blister Label—100mg
1.14.1.1	30-count Blister Label—200mg
1.14.1.1	100-count Bottle Label—25mg
1.14.1.1	100-count Bottle Label—50mg
1.14.1.1	100-count Bottle Label—100mg
1.14.1.1	100-count Bottle Label—200mg
1.14.1.3	Draft Labelling Text
1.14.1.3	Medication Guide

The entire content of this submission is provided on a CD-ROM following ICH eCTD specifications. Signed forms are also provided on paper. One copy of the electronic submission is being provided. This application has been verified and confirmed to be virus-free.

Please contact the undersigned directly with any questions or comments about this submission.

Sincerely,

Tami T. Martin

Tami T. Martin, RN, Esq.
Vice President, Regulatory Affairs
Supernus Pharmaceuticals, Inc.
Phone: 301-838-2607
FAX: 301-424-1364

7 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page.

Supernus Pharmaceuticals, Inc.
1550 East Gude Drive
Rockville, MD 20850
Tel (301) 838-2500
Fax (301) 424-1385

June 17, 2013

Russell G. Katz, M.D., Director
Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research
Office of New Drugs
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA #:	**201635**
Sponsor:	**Supernus Pharmaceuticals, Inc.**
Product:	**SPN-538, Topiramate Extended-Release Capsules**
Sequence #:	**S0036**
Submission Type:	**Response to Request for Information** **Draft Labelling Text** **30-count Blister Commercial Container labels** **100-count Commercial Bottle labels** [redacted] (b) (4) **Medication Guide**

Dear Dr. Katz:

This submission pertains to NDA 201635 which received Tentative Approval on June 7, 2013.

Response to Request for Information

As requested Supernus is providing the current versions of:

- Draft labelling text
- 30-count commercial blister packaging container/closure labels
- 100-count commercial bottle packaging container labels
- [redacted] (b) (4)
- Medication Guide, track change version and clean version

Draft labelling text is unchanged from Sequence 0033, blister packaging configurations are unchanged from Sequence 0034, and bottle labels are unchanged from Sequence 0031; meaning there is no change in any of those items following the June 7, 2013 Tentative Approval.

The Medication Guide has been updated to add current issue dates, remove the header, and add pagination. The content is otherwise unchanged from that agreed upon in June, 2012, and presented in the Tentative Approval at that time. These minor updates are captured in a track change version included in this submission. A clean version of the Medication Guide is also provided.

This official submission is being provided in electronic Common Technical Document (eCTD) format. This submission contains materials for one module:

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Cover letter	
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1.14.1.1	(b) (4)
1.14.1.1	
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1.14.1.1	30-count Blister Label—25mg
1.14.1.1	30-count Blister Label—50mg
1.14.1.1	30-count Blister Label—100mg
1.14.1.1	30-count Blister Label—200mg
1.14.1.1	100-count Bottle Label—25mg
1.14.1.1	100-count Bottle Label—50mg
1.14.1.1	100-count Bottle Label—100mg
1.14.1.1	100-count Bottle Label—200mg
1.14.1.3	Draft Labelling Text
1.14.1.3	Medication Guide

The entire content of this submission is provided on a CD-ROM following ICH eCTD specifications. Signed forms are also provided on paper. One copy of the electronic submission is being provided. This application has been verified and confirmed to be virus-free.

Please contact the undersigned directly with any questions or comments about this submission.

Sincerely,

Tami T. Martin

Tami T. Martin, RN, Esq.
Vice President, Regulatory Affairs
Supernus Pharmaceuticals, Inc.
Phone: 301-838-2607
FAX: 301-424-1364

24 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201635 **INFORMATION REQUEST**

Supernus Pharmaceuticals, Inc.
Attention: Tami T. Martin, VP, Regulatory Affairs
1550 East Gude Drive
Rockville, MD 20850

Dear Ms. Martin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Topiramate Extended Release Capsules, 25 mg, 50 mg, 100 mg, and 200 mg.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

In Amendment #0026 dated January 24, 2013, you provided 30 months stability data on the registration batches of all potency capsules and proposed an expiry date of 30 months for all potency capsules. Include a 30 months testing time point at 25°C/60%RH storage conditions in your post-approval stability testing schedule for first three commercial scale batches as well as the annual commitment batches. Submit the revised post-approval stability protocol within 15 days of the receipt of this letter.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Branch I, Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD
03/18/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201-635

GENERAL ADVICE

Supernus Pharmaceuticals, Inc.
Attention: Tami Martin, RN, Esq.
Vice President, Regulatory Affairs
1150 East Gude Drive
Rockville, MD 20850

Dear Ms. Martin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Trokendi XR (extended release topiramate).

We also refer to your October 31, 2012 submission, which includes your rationale (b) (4) [redacted].

Finally, we refer to your July 24, 2012, meeting request and the meeting between representatives of your firm and the FDA on October 3, 2012, to discuss pediatric labeling for Trokendi XR, and the meeting minutes from that meeting sent to you on December 26, 2012.

We have reviewed the referenced material and have the following comments:

1. (b) (4) [redacted]

   FDA has determined that the protected pediatric information related to the Topamax infant/toddler study is essential to the safe use of topiramate products, including extended release topiramate products. There are statutory and regulatory provisions specific to pediatric uses of drugs that are intended to maximize information available to physicians to treat these vulnerable populations even where the sponsor is not seeking or has not obtained approval for use in those populations. See, 21 USC 355a(j) (requiring drug labeling to include results of pediatric studies conducted under the 505A pediatric exclusivity provisions regardless of whether or not the studies demonstrate the drug is safe or effective in pediatric populations or are inconclusive); see also 21 USC

355A(o)(2) (permitting ANDA labeling to include any appropriate pediatric contraindications, warnings, precautions or other information the Secretary considers necessary to assure safe use in spite of any exclusivity that attaches to that labeling); 21 USC 355c(g)((2) (requiring drug labeling to include results of pediatric studies required under 505B regardless of whether or not the studies demonstrate the drug is safe or effective in pediatric populations or are inconclusive). There are few anti-epileptic drugs approved for use in infants and toddlers, and topiramate is used for seizure control in this age group, even when the products are not labeled for use in this pediatric population. Despite the Trokendi XR warnings against opening the capsule or crushing or chewing it, and labeling indicating use only for children 6 and older, FDA believes that because Trokendi XR will be approved for an indication that occurs in children under age 6, the product will be used in this population. Moreover, because there were adverse events seen in infants and toddlers in the Topamax study that were different from those in older pediatric age groups, the information on use of topiramate in infants and toddlers provided in the Topamax labeling is essential to safe use in this population.

The Topamax infant/toddler study did not establish the effectiveness of the product in this population, but an increased risk of known drug-related adverse reactions, including mortality, were observed. Because of the safety concerns with the use of topiramate in infants and toddlers, clinicians must have access to the available pediatric benefit/risk information for informed prescribing decisions. Thus, we have determined that topiramate products, including those approved under section 505(j) or 505(b)(2) of the FD&C Act, must include the protected infant/toddler pediatric use information for reasons of safe use. While it is generally true that a 505(b)(2) product is not required to have the same labeling as the listed drug, the Agency has determined that the information in this instance is necessary for the safe use of Trokendi XR.

2. (b) (4)

(b) (4)

(b) (4)

[redacted]

For these reasons, the Trokendi XR pediatric use language (b) (4) [redacted] For safety reasons, to convey this pediatric information, you must include the protected Topamax pediatric use language in the Trokendi XR labeling or propose alternative language to fully address the issues above.

If you have any questions, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

RUSSELL G KATZ
01/17/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201-635

MEETING MINUTES

Supernus Pharmaceuticals, Inc.
Attention: Tami Martin, RN, Esq.
Vice President, Regulatory Affairs
1150 East Gude Drive
Rockville, MD 20850

Dear Ms. Martin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trokendi XR (topiramate extended release).

We also refer to your letter dated July 24, 2012, and the meeting between representatives of your firm and the FDA on October 3, 2012. The purpose of the meeting was to discuss the Tentative Approval letter dated June 25, 2012.

Finally, we refer to the Topamax labeling marked to identify the protected pediatric information sent to you on October 4, 2012. At our meeting on October 3, 2012, we indicated that the Agency would identify the sections of the Topamax label protected by pediatric exclusivity. As noted above, the Division sent you this marked up labeling on October 4, 2012.

We appreciate your submission dated October 31, 2012 proposing alternative labeling.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Lana Chen, Regulatory Project Manager at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	**Type C**
Meeting Category:	**End of Review**
Meeting Date:	**October 3, 2012**
Meeting Location:	**FDA White Oak**
Application Number:	**NDA 201-635**
Product Name:	**Trokendi (topiramate)**
Indication:	**Epilepsy**
Sponsor/Applicant Name:	**Supernus**
Meeting Chair:	**Russell Katz, MD**
Meeting Recorder:	**Lana Chen, RPh**

FDA ATTENDEES

Russell Katz, MD, Division Director, DNP
Norman Hershkowitz, MD, PhD Deputy Director, DNP
Lana Chen, RPh, Project Manager, DNP
Jeanine Best, PMHS
Denise Esposito, JD, Deputy Director, ORP
Kalah Auchincloss, JD, ORP
Michael Bernstein, JD, ORP
Elizabeth Dickinson, JD, Chief Counsel, OCC
Kim Dettelbach, JD, OCC
Sonal Vaid, JD, OCC

SPONSOR ATTENDEES

Jack Khattar, CEO, Supernus Pharmaceuticals, Inc.

Stefan Schwabe, MD, PhD, Exec. VP R&D and Chief Medical Officer, Supernus Pharmaceuticals, Inc.

Padmanahb ("Pad") Bhatt, PhD, VP, Drug Development and IP, Supernus Pharmaceuticals, Inc.

Tami Martin, RN, Esq., VP, Regulatory Affairs, Supernus Pharmaceuticals, Inc.

David Clissold, Hyman, Phelps & McNamara, P.C. (Counsel to Supernus Pharmaceuticals, Inc.)

Kurt Karst, Hyman, Phelps & McNamara, P.C. (Counsel to Supernus Pharmaceuticals, Inc.)

DISCUSSION

The purpose of the meeting on October 3, 2012 was to discuss the Tentative Approval letter dated June 25, 2012 and Supernus's correspondence dated July 24, 2012 to Jane Axelrad, JD (Director, Office of Regulatory Policy, CDER, FDA) and Elizabeth Dickinson, JD (Chief Counsel, FDA). According to the June 25, 2012 Tentative Approval letter, final approval of Trokendi may not be made effective until the period of pediatric exclusivity for the listed drug (Topamax) expires. The protected information in question in the Topamax labeling provides safety information in patients 1-24 months of age and is considered necessary for the safe use of Trokendi.

Supernus's July 24 letter requested that FDA reconsider its decision to tentatively approve Supernus's Trokendi, and instead grant full approval of the product for the following reasons:

1. (b) (4)
2.
3.
4.

The Sponsor and Agency discussed each of the points above.

(b) (4)

At our meeting on October 3, 2012, the Agency stated that the protected information in the Topamax labeling is necessary for the safe use of Trokendi.

(b) (4)

At the meeting, we also stated that the Agency would identify the sections of the Topamax labeling protected by pediatric exclusivity, to help Supernus understand what substantive information must be included in the Trokendi labeling.

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/s/

RUSSELL G KATZ
12/26/2012

Chen, Lana Y

From: Chen, Lana Y
Sent: Monday, December 10, 2012 2:15 PM
To: Tami Martin
Cc: Chen, Lana Y
Subject: RE: Blister package for NDA 201635 and effect on Tentative Approval

Hello Tami,

On our initial examination, we find that the new Blister Package configuration is adequate. However, you must formally submit this as an amendment to the NDA. You can submit this anytime; but, we recommend that it be submitted sooner then later. This amendment will not hold up the schedule for the final approval of the Trokendi NDA.

thanks,
Lana

****

Lana Y. Chen, R.Ph., CAPT-USPHS
Senior Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research, FDA
Phone 301-796-1056
Fax 301-796-9842
Email: **lana.chen@fda.hhs.gov**

From: Tami Martin [mailto:tmartin@supernus.com]
Sent: Tuesday, November 20, 2012 2:40 PM
To: Tami Martin; Chen, Lana Y
Subject: Blister package for NDA 201635 and effect on Tentative Approval

Hello Capt. Chen,

We have nearly completed preparations concerning a blister configuration package for the topiramate extended-release capsule, so that we could re-introduce a 30-count commercial package [redacted] (b) (4) for regulatory review under NDA 201635.

I would like to understand our opportunities for submitting this information. Please see highlighted section in this e mail string, on July 12, 2012. If we were to submit a 30-count amendment to the NDA at this time would it

1) Likely require a 6 month review?
2) Halt our discussions about the legal/policy points concerning issuance of a full, instead of a tentative approval (Reference meeting of October 3, 2012 and recent submission regarding new reference sources for protected language)?
3) I understand that such a submission allows the agency to set a new response date. What exactly happens to the tentative approval in this situation? Is it rescinded or withdrawn or does it remain in place if changes are for a

new commercial package?

> We want to submit the blister configurations as an amendment, but we do not want to endanger the issuance of a full approval letter after the expiration of pediatric exclusivity in June 2013. Depending on what you tell us, we may opt to supply these materials as a supplement post approval rather than as an amendment to the current file.

Any insight you can give about the review process that would take place with such an amendment, and what effect this would have on our Tentative Approval status would be appreciated.

Tami Martin
301-838-2607
tmartin@supernus.com

From: Tami Martin
Sent: Wednesday, August 22, 2012 1:47 PM
To: 'Lana.Chen@fda.hhs.gov'
Subject: Re: FDA follow-up re: NDA 201635--revised blister pack configurations and usability protocol

Team response: We don't have a full set of all prototypes but have some untouched items. I can describe in more detail if that is of immediate interest. Otherwise we would have to work with vendor to get more prototypes.

Tami Martin

From: Tami Martin
To: 'Lana.Chen@fda.hhs.gov'
Sent: Wed Aug 22 13:32:01 2012
Subject: Re: FDA follow-up re: NDA 201635--revised blister pack configurations and usability protocol

We'll have to have more prototypes made, I think. Let me check with team.

Tami Martin

From: Chen, Lana Y
To: Tami Martin
Cc: Chen, Lana Y ; Kelley, Laurie
Sent: Wed Aug 22 12:27:37 2012
Subject: RE: FDA follow-up re: NDA 201635--revised blister pack configurations and usability protocol

Hi Tami,

If possible, please send 2 desk copies to:

Julie Neshiewat
Safety Evaluator
Division of Medication Error Prevention and Analysis
CDER, Office of Surveillance and Epidemiology
10903 New Hampshire Ave.
Building 51, Room 6263
Silver Spring, MD 20993

thanks,
Lana

From: Tami Martin [mailto:tmartin@supernus.com]
Sent: Tuesday, August 21, 2012 1:22 PM
To: Chen, Lana Y
Subject: RE: FDA follow-up re: NDA 201635

Hello Capt. Chen

We are ready to send in the revised blister pack configurations and usability protocol to the (paper) IND for topiramate extended release capsules, IND 101670.

I was preparing to send it to the Ammendale address; I did try to reach you by phone to see if you'd prefer to receive them at White Oak. I am going to hold off about an hour to see if you get this message and state a preference, otherwise please look for them delivered to the Ammendale address by FED EX for your receipt tomorrow.

Tami

From: Chen, Lana Y [mailto:Lana.Chen@fda.hhs.gov]
Sent: Thursday, July 19, 2012 2:55 PM
To: Tami Martin
Cc: Chen, Lana Y
Subject: RE: FDA follow-up re: NDA 201635

Hi Tami,

Please submit your revised blister packaging configuration and usability protocol to the IND. Once all materials are submitted, the Agency will need two months to conduct a review.

Look forward to working with you.

thanks,
Lana

****

Lana Y. Chen, R.Ph., CAPT-USPHS
Senior Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research, FDA
Phone 301-796-1056
Fax 301-796-9842
Email: **lana.chen@fda.hhs.gov**

From: Ware, Jacqueline H
Sent: Wednesday, July 18, 2012 10:05 AM
To: Chen, Lana Y
Subject: FW: FDA follow-up re: NDA 201635

From: Tami Martin [mailto:tmartin@supernus.com]
Sent: Thursday, July 12, 2012 4:19 PM
To: Ware, Jacqueline H
Subject: RE: FDA follow-up re: NDA 201635

Hello Capt. Ware

We think that in about 4-6 weeks from now we can provide a new blister configuration prototype which will include (b) (4) foil and a (b) (4) card design. Capsules will be in a (b) (4). The package will not have artwork. We can provide proposed opening instructions separately.

We would like to submit this prototype to you for your review. After you have had that opportunity to evaluate its functionality, we hope to speak further about the most reasonable way to complete our work so that we could include the 30 count blister configuration in what we anticipate with be a full approval once market exclusivity provisions for 1-24 month olds are no longer in effect (this market exclusivity expires June 22, 2013). With a Tentative Approval, may I still do Sequence submissions to the NDA prior to sending in the final item which I would characterize as the "(final) Resubmission document"? I have not been under a Tentative Approval before, so I'm not clear how this should work. At one point, we spoke about submitting the usability protocol to the IND, so I'd like to understand if review can continue under the NDA until we feel we have provided a full "resubmission" or if we must revert back to the IND for any continuing discussions. Remembering that the IND for this program is a paper IND, I think it would be easier to continue under the (electronic) NDA, so that is another reason for my query.

Another question, if we seek to add the 30 count blister configuration package back into the NDA as part of a (presumably) Class II resubmission on or around November, 2012, it seems like we should expect about a 6 month review, taking us to May 2013. If we then we also wanted to update the NDA with 30 month real time stability data in January 2013, what type of submission would that be? A Class I resubmission? Or a simple amendment to a pending NDA by Sequential submission? Or would you recommend to hold stability data for submission in an Annual Report? I don't want to do anything, of course, that will impair our ability to be eligible for a full approval come June 23, 2013.

Thank you for any insight you can give me as to our plans for continuing this discussion on the 30 count commercial package (b) (4) for SPN-538/NDA 201635, and for any advice about continuing sequential submissions after a TA action letter.

Tami Martin

From: Ware, Jacqueline H [mailto:Jacqueline.Ware@fda.hhs.gov]
Sent: Friday, July 06, 2012 2:38 PM
To: Tami Martin
Cc: Ware, Jacqueline H
Subject: FDA follow-up re: NDA 201635

Dear Ms. Martin,

CDER's Division of Medication Error Prevention and Analysis has the following question and comments

regarding your revised blister packaging configuration.

- When can we expect to receive the mock-up of the revised blister packaging configuration. Submitting without artwork is fine at this time, but DMEPA will need to evaluate the artwork when it is available. DMEPA is not be able to provide comments on their usability study protocol until a mock-up of the revised blister packaging configuration is received.

An email response to this inquiry is sufficient.

Many thanks,
Jackie Ware

****

Jacqueline H. Ware, Pharm.D., RAC
Captain, United States Public Health Service
Supervisory Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4346
Silver Spring, MD 20993-0002
phone: 301-796-1160
fax: 301-796-9842
email: jacqueline.ware@fda.hhs.gov

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/s/

LANA Y CHEN
12/10/2012
with concurrence from Russell Katz, MD, Division Director, DNP

Chen, Lana Y

From: Kurt R. Karst [KKarst@hpm.com]
Sent: Friday, September 14, 2012 2:53 PM
To: Vaid, Sonal
Cc: Dave B. Clissold
Subject: Supernus FDA Meeting

Sonal:

I checked with the folks at Supernus and Oct. 3rd from 10-11 AM works for a meeting. I will send you a list of attendees once I have them. One Supernus attendee might be a foreign national. Do you need any additional information in that case? Is the meeting at White Oak? Also, please send me a list of anticipated FDA attendees once you have them.

Thank you! Have a great weekend.

Kurt

Kurt R. Karst
Hyman, Phelps & McNamara, P.C.
www.hpm.com
700 13th Street, N.W., Suite 1200
Washington, D.C. 20005
(T) 202.737.7544
(F) 202.737.9329
kkarst@hpm.com
Visit the HPM FDA Law Blog: www.fdalawblog.net

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/s/

LANA Y CHEN
11/14/2012
Placed in DARRTS on behalf of OCC

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Tami T. Martin, RN, Esq.
Vice President, Regulatory Affairs
Supernus Pharmaceuticals, Inc.
1550 East Gude Drive
Rockville, MD 20850

RE: NDA # 201635
Trokendi XR (topiramate) extended-release capsules
MA #1

Dear Ms. Martin:

This letter responds to Supernus Pharmaceuticals, Inc. (Supernus) submission dated September 11, 2012, requesting the review of the proposed "Coming Soon" ad panel for Trokendi XR (topiramate) extended-release capsules (Trokendi XR).

We acknowledge that your cover letter states, "Supernus Pharmaceuticals, Inc. has received a tentative approval on topiramate extended-release capsules (Trokendi XR™, NDA 201635, expected full approval June 23, 2013 upon expiration of Topamax® market exclusivity protections)."

The Division of Professional Drug Promotion (DPDP) in the Office of Prescription Drug Promotion (OPDP) has reviewed the proposed coming soon ad panel for Trokendi XR and has no comment at this time.

If you have any questions or comments, please direct your response to the undersigned by facsimile at (301) 847-8444, or at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Professional Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266.** Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, Division of Professional Drug Promotion (DPDP), and the Division of Consumer Drug Promotion (DCDP). To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to the MA # 1 in addition to the NDA number in all future correspondence relating to this particular matter. DPDP reminds you that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Quynh-Van Tran, PharmD, BCPP
Regulatory Review Officer
Division of Professional Drug Promotion
Office of Prescription Drug Promotion

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/s/

QUYNH-VAN TRAN
10/26/2012

From: Neshiewat, Julie
To: Ware, Jacqueline H
Cc: Kelley, Laurie; Chan, Irene Z.
Subject: RE: NDA 201635 Revised bottle label
Date: Friday, June 22, 2012 2:47:00 PM

Hi Jackie:

DMEPA has reviewed the revised Trokendi XR labels, and we do not have any additional recommendations at this time. Thank you.

Julie Villanueva Neshiewat, PharmD
Safety Evaluator
Division of Medication Error Prevention and Analysis

From: Ware, Jacqueline H
Sent: Friday, June 22, 2012 1:30 PM
To: Neshiewat, Julie
Cc: Kelley, Laurie
Subject: Fw: NDA 201635 Revised bottle label

Julie,
See attached from Supernus. Please say that these are ok. Thx! Jackie

---

From: Tami Martin [mailto:tmartin@supernus.com]
Sent: Friday, June 22, 2012 01:28 PM
To: Ware, Jacqueline H
Subject: NDA 201635 Revised bottle label

Dear Capt Ware,

Please find attached NDA 201635 bottle labels, revised as directed. We have corrected the year graphic to allow for a 4 digit year on expiration dating. In addition, just to differentiate them from the earlier version sent on 6-20, we have changed revision date to 22June2012.

We consider these to be the agreed-upon bottle labels for Trokendi XR™ NDA 201635.

Tami Martin, RN, Esq.
Vice President, Regulatory Affairs
Supernus Pharmaceuticals, Inc.
Ph: 301-838-2607
mailto:tmartin@supernus.com

4 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

JULIE V NESHIEWAT
06/22/2012

IRENE Z CHAN
06/25/2012

Ware, Jacqueline H

From:	Ware, Jacqueline H
Sent:	Wednesday, June 06, 2012 4:28 PM
To:	'Tami Martin'
Cc:	Ware, Jacqueline H
Subject:	FDA Proposed Draft Labeling for NDA 201-635/Trokendi XR (topiramate extended-release) Capsules
Attachments:	6.6.12 FDA Proposed MG text_NDA 201635 TROKENDI XR.doc; 6.6.12 FDA Proposed Labeling Text_NDA 201635 TROKENDI XR.doc

Dear Ms. Martin,

Please refer to your August 30, 2011 New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Trokendi XR (topiramate extended-release) Capsules.

We also refer to our November 14, 2011 letter in which we notified you of our target date of June 11, 2012 for communicating labeling changes and/or post-marketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

Attached please find FDA's proposed draft labeling ("clean" WORD documents for the Package Insert and Medication Guide) for Trokendi XR (topiramate extended-release) Capsules. The base document used for FDA's proposal is Supernus' labeling submitted on August 30, 2011. FDA's labeling has been reviewed and cleared to the level of Division Director.

Please share this proposed labeling with the appropriate people on your team and let me know if it is acceptable. If you wish to send a counter-proposal, please provide it via email as a tracked-changes WORD document using our proposed labeling as the base.

Please note that FDA's proposed draft labeling includes and excludes specific language that has exclusivity protection in Topamax labeling (the RLD for the Trokendi XR NDA). Because some of the labeling necessary for the safe use of the product is protected by exclusivity, your application may not be eligible for a full approval until relevant exclusivity protection expires.

Lastly, we are targeting June 25, 2012 as the action date for this application. As such, we ask that you please respond to this email by 12:00 pm on Tuesday, June 12, 2012.

If you have any questions, please let me know.

Kind regards,
Jackie Ware

****

Jacqueline H. Ware, Pharm.D., RAC
Captain, United States Public Health Service
Senior Regulatory Project Manager

Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4346
Silver Spring, MD 20993-0002

phone: 301-796-1160
fax: 301-796-9842
email: jacqueline.ware@fda.hhs.gov

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/s/

JACQUELINE H WARE
06/24/2012

MEMORANDUM OF TELECON

DATE: June 19, 2012

APPLICATION NUMBER: NDA 201635

BETWEEN:

Supernus Pharmaceuticals:
Tami Martin, RN, Esq., Vice President, Regulatory Affairs
Padmanabh Bhatt, Ph.D., Sr. Vice President, Intellectual Property and Chief Scientific Officer

AND

ONDQA:
Richard Lostritto, Ph.D., Acting Deputy Director for Science and Policy and Acting Biopharmaceutics Lead
Angelica Dorantes, Ph.D., Biopharmaceutics Team Leader
Arzu Selen, Ph.D., Biopharmaceutics Research Lead
Martha Heimann, Ph.D., CMC Lead
Thomas Wong, Ph.D., Review Chemist
Teshara G. Bouie, Project Manager

SUBJECT: Dissolution Acceptance Criteria

Background:
On June 6, 2012 the Agency sent the sponsor the following information request:

Please revise the dissolution acceptance criteria for the Trokendi XR capsules from (b) (4) *of the label claim dissolved at* (b) (4) *to* (b) (4) *of the label claim dissolved at 6 hrs" for the 25-, 50-, 100- and 200-mg strengths of the Trokendi XR capsules. Please revise the dissolution acceptance criteria in the drug product specification list to reflect this change and submit the revised specification list by June 11, 2012.*

The sponsor proposed to accept the Agency's dissolution acceptance criteria on an interim basis for one year. The Agency agreed. The following additional information request was sent on June 14, 2012:

1. *Your proposal of setting the dissolution acceptance criteria for your product on an interim basis for one year is acceptable. Please provide the updated specification Table for your product with the revised dissolution criteria.*

2. *Additionally, we remained most concerned regarding the three (3) hour time point dissolution limits which appear to be set wide based on between batch variability. We the dissolution data between batches and that you have implemented a corrective action which is expected to*

minimize between batch variability in commercial manufacturing. Therefore, for the setting of the final dissolution acceptance criteria, we request that you agree to the following:

- *To collect additional dissolution profile data for the commercial validation batches (each strength) manufactured during the first year after the action date, targeting more appropriate acceptance criteria in alignment with the FDA standards described in IVIVC-Guidance Section B-1 (Setting Dissolution Specifications without an IVIVC).*
- *To use the additional dissolution data generated from the commercial validation batches for the setting of the final acceptance criteria.*
- *To submit a prior approval supplement to the NDA within 14 months from the action date, including a proposal for the final acceptance criteria and the supportive dissolution data (each strength) from the commercial validation batches which are based on and reflective of the data discussed herein.*

The Call:

- Supernus stated they are currently producing validation batches and commercial launch supplies and questioned if any lots fail to meet the interim specification of (b) (4) at 6 hour will the Agency be open to dialogue so they have an opportunity to change the specification. The Agency responded that based on the data provided in the NDA, a batch failing at Q= (b) (4) at 6 hours does not appear likely. However, the Agency is always open to discuss any batch that fails to meet a specification. The sponsor would have to justify why regulatory discretion should be allowed.

- Supernus committed to revising the dissolution specification table in section 3.2.P.5.1 by June 21, 2012.

- Supernus requested clarification regarding the prior approval supplement to be submitted within 14 months of the action date. The sponsor will collect data for 12 months and have 2 months to submit the supplement.

- The Agency advised the sponsor to target a narrower range at the 3 hour time point.

- For the 3 hour specification-time point, Supernus was advised to target mean (b) (4) for the collection of the dissolution data. Specifically, if L1 (n=6) fails the (b) (4) specification range, proceed to L2 (n=12) testing, then to L3 (n= 24) if necessary.

_____

Teshara G. Bouie
Regulatory Health Project Manager

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/s/

TESHARA G BOUIE
06/21/2012

Bouie, Teshara

From: Bouie, Teshara
Sent: Thursday, June 14, 2012 9:51 AM
To: Tami Martin
Cc: Ware, Jacqueline H
Subject: RE: NDA 201635

Hi Tami,

1. Your proposal of setting the dissolution acceptance criteria for your product on an interim basis for one year is acceptable. Please provide the updated specification Table for your product with the revised dissolution criteria.

2. Additionally, we remained most concerned regarding the three (3) hour time point dissolution limits which appear to be set wide based on between batch variability. We the dissolution data between batches and that you have implemented a corrective action which is expected to minimize between batch variability in commercial manufacturing. Therefore, for the setting of the final dissolution acceptance criteria, we request that you agree to the following:

   - To collect additional dissolution profile data for the commercial validation batches (each strength) manufactured during the first year after the action date, targeting more appropriate acceptance criteria in alignment with the FDA standards described in IVIVC-Guidance Section B-1 (Setting Dissolution Specifications without an IVIVC).
   - To use the additional dissolution data generated from the commercial validation batches for the setting of the final acceptance criteria.
   - To submit a prior approval supplement to the NDA within 14 months from the action date, including a proposal for the final acceptance criteria and the supportive dissolution data (each strength) from the commercial validation batches which are based on and reflective of the data discussed herein.

Regards,

Teshara G. Bouie

From: Tami Martin [mailto:tmartin@supernus.com]
Sent: Friday, June 08, 2012 4:40 PM
To: Bouie, Teshara
Cc: Ware, Jacqueline H
Subject: RE: NDA 201635

Hello Ms. Bouie and Capt. Ware,
Our internal team wanted to send you this specific response to your request to revise the dissolution acceptance criteria, please see below in quotes:
"We tentatively accept your proposal and would like to accept these specifications on an interim basis for 1 year. We are currently in the process of validating 3 commercial batches for each strength. We will assess the ability of these batches to meet the revised specifications over the next 6-9 months. In the event that these batches fail to meet this revised interim dissolution acceptance criteria at the 6 hour time point, we would like to have the opportunity to dialog with the FDA to revert back to our originally proposed dissolution acceptance criteria at the (b)(4) hour time point. If the Agency agrees with this approach, we will submit the revised interim dissolution acceptance criteria in the drug product specification list. We are also open to discuss this further in a teleconference with the FDA, if you desire, at your earliest convenience."
My thinking is that this is not unusual -- you set your specification but as you gain more experience with your

manufacture, you may wish to re-approach the agency to consider revised specifications. Please let us know that you agree that this is reasonable, and if so, we will submit revised dissolution acceptance criteria as indicated above.

Thank you. If you have no issues with this approach, I will prepare the revised specifications for submission early next week to get them to you ASAP.

Tami Martin
Supernus Pharmaceuticals, Inc.
301-838-2607

From: Bouie, Teshara [mailto:Teshara.Bouie@fda.hhs.gov]
Sent: Wednesday, June 06, 2012 2:54 PM
To: Tami Martin
Cc: Ware, Jacqueline H
Subject: NDA 201635

Hi Tami,

Please revise the dissolution acceptance criteria for the Trokendi XR capsules from (b) (4) of the label claim dissolved at (b) (4) to (b) (4) of the label claim dissolved at 6 hrs" for the 25-, 50-, 100- and 200-mg strengths of the Trokendi XR capsules. Please revise the dissolution acceptance criteria in the drug product specification list to reflect this change and submit the revised specification list by June 11, 2012.

Regards,

Teshara G. Bouie, MSA, OTR/L
CDR, United States Public Health Service
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment I
Phone (301) 796-1649
Fax (301) 796-9749

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/s/

TESHARA G BOUIE
06/14/2012

Bouie, Teshara

From: Bouie, Teshara
Sent: Wednesday, June 06, 2012 2:54 PM
To: Tami Martin
Cc: Ware, Jacqueline H
Subject: NDA 201635

Hi Tami,

Please revise the dissolution acceptance criteria for the Trokendi XR capsules from (b) (4) of the label claim dissolved at (b) (4) to (b) (4) of the label claim dissolved at 6 hrs" for the 25-, 50-, 100- and 200-mg strengths of the Trokendi XR capsules. Please revise the dissolution acceptance criteria in the drug product specification list to reflect this change and submit the revised specification list by June 11, 2012.

Regards,

Teshara G. Bouie, MSA, OTR/L
CDR, United States Public Health Service
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment I
Phone (301) 796-1649
Fax (301) 796-9749

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/s/

TESHARA G BOUIE
06/06/2012

Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Thursday, May 24, 2012 3:43 PM
To: 'Tami Martin'
Cc: Ware, Jacqueline H
Subject: FDA Comments re: NDA 201635

Dear Tami,

Below are carton and container comments from the review team related to their ongoing review of NDA 201635/Trokendi XR capsules. Please note that, while the below includes comments on the blister cards, the design and usability issues (previously discussed with you) remain a significant concern.

A. Packaging design of blister card labeling
The removal of numbering [redacted] (b) (4) on the blister cards proposed by the Applicant will need to be implemented for the 30-count retail [redacted] (b) (4) blister cards.

Additionally, the design of the blister cards is confusing [redacted] (b) (4) The blister cards should be redesigned with a packaging configuration that presents the medication in a linear manner and does not infer varying doses.

Moreover, it is difficult to access the medication through the blister card labeling. A majority of the cardboard is left intact and the medication cannot be pushed through the foil. Additionally, even after multiple attempts in peeling the cardboard tab off, it is difficult to push the capsule through the foil without crushing it. When the capsule is crushed, the contents inside the capsule can come out of the capsule. Given these problems with the proposed blister card labeling, a usability study to verify that patients can access the medication is needed.

B. Container Labels, Blister Card Labeling: 30-count retail, [redacted] (b) (4)

1. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
2. To help distinguish this extended-release product from the marketed immediate-release topiramate products, add a descriptor indicating that the product should be dosed "Once Daily" and administration instructions to "**Swallow whole and intact.** Do not open, crush, chew, or sprinkle capsule contents on food." These statements should appear on the principle display panel.
3. Remove the circular graphic that appears above "XR." This graphic detracts from the proprietary name, active ingredient, and strength statement.

4. Remove the blue background found on the bottom half portion of the principal display panel, since it makes the four strengths appear similar to one another and increases the risk that the wrong strength is dispensed to patients.
5. Revise the presentation of "EXTENDED-RELEASE" from all upper case to title case "Extended-release" to improve readability.
6. Add a statement to the principal display panel instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed per 21 CFR 208.24.
7. Decrease the size of the Supernus Pharmaceuticals logo since it detracts from the proprietary name, active ingredient, and strength.
8. In order to accommodate the "Once Daily" and "**Swallow whole and intact.** Do not open, crush, chew, or sprinkle capsule contents on food," relocate the "Rx only" statement to the bottom right corner.

C. Blister Card Labeling: 30-count retail

1. In some instances, the strength with units does not appear within the same line of text. Revise the strength presentation to ensure the units appear next to the number to improve readability.
2. Revise the strength presentation from XX mg to read "XX mg per capsule." As currently presented, it is unclear if the total contents of the sample blister card is XX mg or if the contents per capsule is XX mg. If a patient interprets XX mg as the total contents of the blister card instead of the contents of one capsule, an overdose error will occur.
3. Add a statement declaring the presence of FD&C Yellow No. 6 on the blister card labeling for the 50 mg, 100 mg, and 200 mg capsules per 21 CFR 201.20(c).
4. There should be sufficient drug information on all panels of the blister cards in the case that the blister cards are separated from each other. Add the proprietary name and established name to appear with the strength on Panels A, B, D, and E.
5. The blister card labeling designates a space for the package insert, but it does not designate a space for the placement of a pharmacy label. Indicate a designated space to affix the pharmacy prescription label.

D. (b) (4)

Please provide written responses and revised draft labeling (similar in format to that submitted 2/3/12) that address these comments via a formal submission in archival format as an amendment to the above NDA. It is

acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

We ask that you please respond to this comments by June 7, 2012. If a response by then is not feasible, please contact me to discuss further.

If you have any questions, please let me know.

Thank you,
Jackie

****

Jacqueline H. Ware, Pharm.D., RAC
Captain, United States Public Health Service
Senior Regulatory Project Manager

Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4346
Silver Spring, MD 20993-0002

phone: 301-796-1160
fax: 301-796-9842
email: jacqueline.ware@fda.hhs.gov

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/s/

JACQUELINE H WARE
05/24/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 201635

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Supernus Pharmaceuticals, Inc
1550 East Gude Drive
Rockville, MD 20833

ATTENTION: Tami T. Martin, RN, Esq.
Vice President, Regulatory Affairs

Dear Ms. Martin:

Please refer to your New Drug Application (NDA) submitted January 13, 2011 and received January 14, 2011, under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for topiramate extended release capsules, 25 mg, 50 mg, 100 mg, and 200 mg.

Please also refer to your resubmission dated August 30, 2011, received September 9, 2011. We also refer to your correspondence submitted January 16, 2012, received January 17, 2012, requesting review of your proposed proprietary name, Trokendi XR.

We have completed our review of the proposed proprietary name Trokendi XR and have concluded that it is acceptable. If **any** of the proposed product characteristics as stated in your January 16, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

The proposed proprietary name, Trokendi XR, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Jacqueline Ware at (301) 796-1160.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TEENA THOMAS
04/13/2012

CAROL A HOLQUIST
04/13/2012

From: Tami Martin
To: Parncutt, Stephanie
Subject: RE: FDA Request for Information - NDA 2021635/Trokendi (topiramate extended-release) Capsules
Date: Tuesday, April 03, 2012 12:22:34 PM

OK, not only because of your name associated with the e mail, but also because the document content talks about a tablet, and the NDA 201635 is a capsule, so I was concerned there was some cross-NDA activity. Thanks for the clarification. We'll proceed with the comments as pertaining to NDA 201635.

Tami Martin

From: Parncutt, Stephanie [mailto:Stephanie.Parncutt@fda.hhs.gov]
Sent: Tuesday, April 03, 2012 12:10 PM
To: Tami Martin
Subject: RE: FDA Request for Information - NDA 2021635/Trokendi (topiramate extended-release) Capsules

Tami,

I'm covering this application for Jackie Ware this week, while she is out on leave. The attachment does pertain to NDA 201-635/Trokendi (topiramate extended-release) Capsules. I just wanted to confirm that with you in response to your recent voicemail message. Thank you,

Stephanie

---

tephanie
ril 03, 2012 11:44 AM

eline H
Request for Information - NDA 2021635/Trokendi (topiramate extended-release) Capsules
gh

Attached is a request from the Pediatric and Maternal Health Staff & Clinical team related to their ongoing review of the Trokendi application (N 201-635). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to Jackie Ware and myself in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

* Please see the attachment below from the Pediatric and Maternal Health Staff & Clinical team reviewers:

<< File: NDA 201635 PREA IR.doc >>

Please respond to this request in the timeframe requested in the attachment; if you are unable to meet this timeframe, please contact myself or Jackie Ware to discuss.

~~~~~~~~~~~~~~~~~~~~~~~~~~

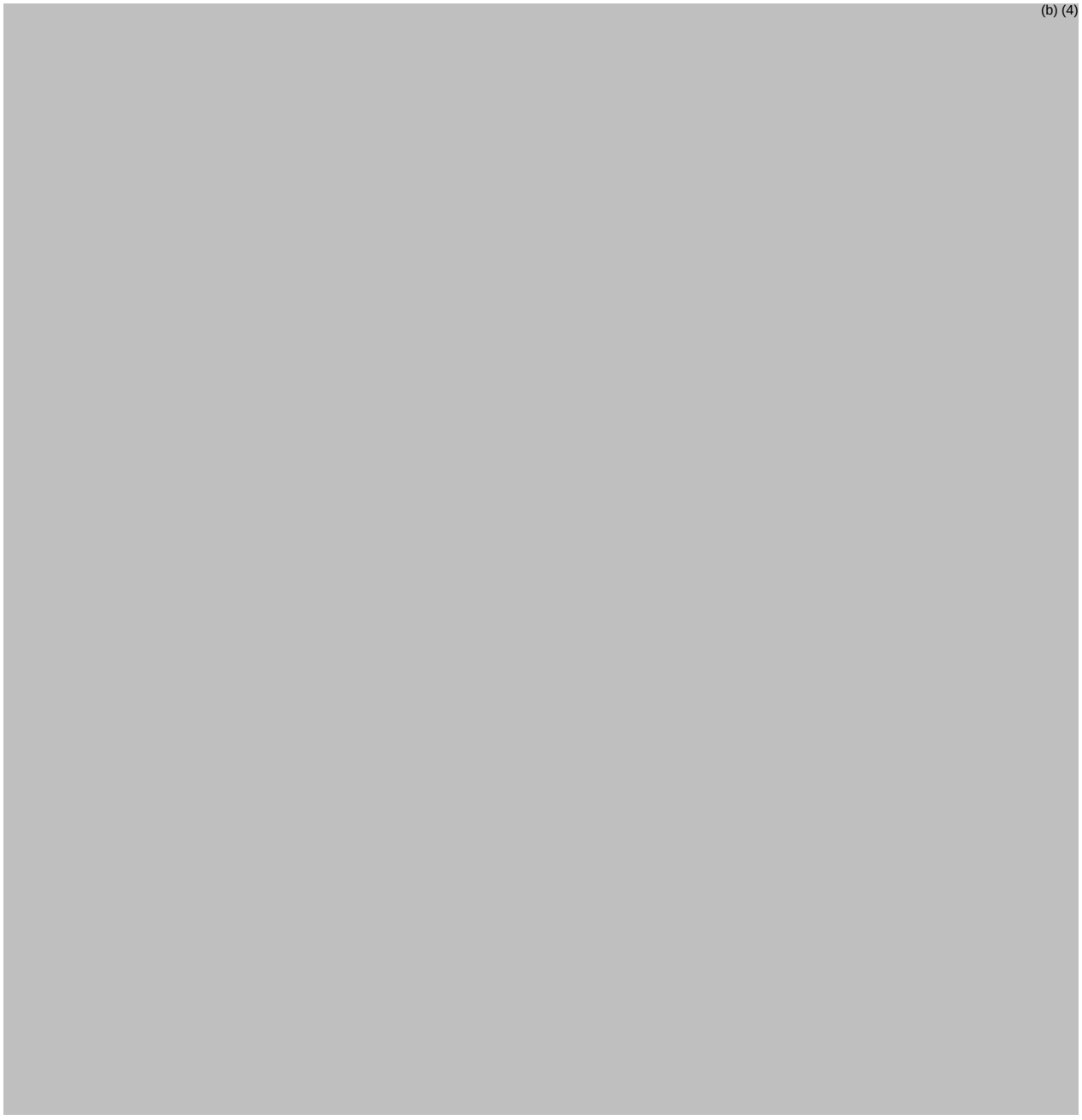
Stephanie N. Parncutt
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4355
Silver Spring, MD 20993-0002

phone: 301-796-4098
~~~~~~~~~~~~~~~~~~~~~~~~~~

email: stephanie.parncutt@fda.hhs.gov

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

(b) (4)



Please take these comments into consideration and submit a pediatric plan. This plan must outline the age groups and the pediatric studies (e.g., pharmacokinetics/ pharmacodynamics, safety, and efficacy) that you plan to conduct to meet the PREA requirements. A pediatric plan is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetics/ pharmacodynamics, safety, efficacy) sufficient to demonstrate dose, safety, and efficacy. The pediatric plan must contain a timeline for the completion of pediatric studies, i.e. the dates of (1) protocol submission, (2) study completion and (3) submission of study reports. In addition, you must submit certification of the grounds for deferral and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time. (See Draft Guidance for Industry, How to Comply with Pediatric Research Equity Act, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079756.pdf).

Please note that we would agree to a partial waiver request for pediatric patients birth to one month because the study would be impossible or highly impractical because there are too few patients with this disorder to make such a study practicable. Should you decide to pursue a partial waiver for pediatric patients over one month of age, you must provide us with documentation and data to support your request.

Please respond with your pediatric plan within 4 weeks from this letter date.

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/s/

STEPHANIE N PARNCUTT
04/03/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201635 **GENERAL ADVICE**

Supernus Pharmaceuticals, Inc.
Attention: Tami T. Martin, VP, Regulatory Affairs
1550 East Gude Drive
Rockville, MD 20833

Dear Ms. Martin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Topiramate Extended Release Capsule, 25 mg, 50 mg, 100 mg, and 200 mg.

We also refer to your January 18, 2012 submission, requesting feedback on your proposal to change the encapsulation MBRs (b) (4) .

We have reviewed the referenced material and have the following responses to your questions.

Question 1:
For NDA approval purposes, would the FDA accept results from validation batches made from a (b) (4) *batch size as long as there is no change in process?*

FDA Response:
It should be noted that the Agency does not currently require validation of the proposed commercial manufacturing process prior to the approval of the NDA. Additionally, FDA does not approve process validation approaches, protocols, or specific batches used in process validation studies. The actual protocols, acceptance criteria and study outcomes will be evaluated during an inspection. It is, however, the expectation of the Agency that Stage 2 Process Validation should be completed prior to the decision to release product for commercial distribution.

With respect to the question of (b) (4) batch sizes for commercial production, the process validation guidance states, "The decision to begin commercial distribution should be supported by data from commercial-scale batches." The data used to support the release and distribution of these commercial batches should come from production batches, including those *of that same scale*. Data from laboratory and pilot studies can be used to provide supplementary assurance that the commercial manufacturing process performs as expected. See Section IV.C.2 of the 2011 Guidance for Industry on Process Validation for additional recommendations on how to document this stage of your process validation.

It should be noted that it is a CGMP expectation that batch sizes be documented in the preparation of master production and control records (21 CFR 211.186). Such records should clearly identify the batch sizes that are approved for commercial operations by the firm's Quality Unit.

Please find more information in the Guidance for Industry, *Process Validation: General Principles and Practices* (January 2011):

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf

Any additional questions regarding Process Validation can be addressed to the CDER Office of Compliance via the contacts listed in the Federal Register for this guidance (**Federal Register** / Vol. 76, No. 16 / Tuesday, January 25, 2011 / Notices).

Question 2:
If yes, would an NDA amendment changing the (b) (4) *encapsulation MBRs* (b) (4) *be required?*

FDA Response:
It is necessary to amend the commercial encapsulation MBRs (b) (4) that may be manufactured for commercial distribution.

Question 3:
If an amendment is required, would it be expected to extend the review and/or the PDUF A date set for this New Drug Application?

FDA Response:
If the amended commercial encapsulation MBRs are submitted prior to the end of April, it would not extend the review and PDUFA dates.

Question 4:
If the FDA is agreeable to (b) (4) *batch sizes for process validation, please confirm that this would mean that the FDA would also permit* (b) (4) *batch sizes for commercial batches of our product?*

FDA Response:
See response to question #1.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.

Branch Chief
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD
03/14/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201635 **INFORMATION REQUEST**

Supernus Pharmaceuticals, Inc.
Attention: Tami T. Martin, VP, Regulatory Affairs
1550 East Gude Drive
Rockville, MD 20833

Dear Ms. Martin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Topiramate Extended Release Capsules, 25 mg, 50 mg, 100 mg, and 200 mg.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Designate one of the test methods, TM-538-104 or TM-538-105, as the regulatory method for the quantification of (b) (4) content in the drug product specification. The other method can be an alternate method.
2. Provide justification of (b) (4) in the drug product specification based on safety consideration.
3. In the labeling text, you need to mention the presence of FD&C Yellow No. 6 in the capsule shells that contain this colorant according to CFR 201.20 (c).

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD
03/14/2012

Supernus Pharmaceuticals, Inc.
1550 East Gude Drive, Rockville, MD 20850 USA
Phone: 301.838.2500 Fax: 301.424.1364
www.supernus.com

Supernus® Pharmaceuticals

NDA 201635
PATENT AMENDMENT

February 23, 2012

Russell Katz, M.D., Director
Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research
Office of New Drugs
Food and Drug Administration
5901-B Ammendale Road
Beltsville MD 20705-1266

RE: NDA 201635
Patent Amendment
Topiramate Extended Release Capsules, 25mg, 50mg, 100mg, 200mg

Dear Sir:

This letter provides notification to the Agency, pursuant to 21 C.F.R § 314.107, documenting that Supernus Pharmaceutical Inc. ("Supernus") has not been sued within the 45 day period since providing its Paragraph IV notice for Topiramate Extended Release Capsules (NDA 201635).

Supernus' 505(b)(2) NDA for Topiramate Extended Release Capsules (NDA 201635) contained one Paragraph IV certification. Supernus complied with the notice requirements in its November 22, 2011 letter.

In accordance with 21 C.F.R. § 314.52(e), documentation of receipt of notice has been provided by way of a copy of the certified mail receipt showing delivery dated November 28, 2011 to Janssen Pharmaceuticals, Inc. (NDA holder) and dated November 28, 2011 to Johnson & Johnson (patent owner) (copies attached).

Since providing the above described notice, the 45 day period has expired and Supernus was not sued by the NDA holder or patent owner identified above. Therefore, Supernus believes it is eligible for immediate final approval of its 505(b)(2) NDA as soon as FDA is able to adequately address and resolve all scientific issues related to the application.

If you have any questions or concerns with regard to the presented information please do not hesitate to contact me at 301-838-2630.

Sincerely,

Padmanabh P. Bhatt, Ph.D.
Vice President of Pharmaceutical Sciences
Supernus Pharmaceuticals, Inc.

Attachments

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 201635

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Supernus Pharmaceuticals, Inc
1550 East Gude Drive
Rockville, Maryland 20833

ATTENTION: Tami T. Martin, RN, Esq.
Vice President, Regulatory Affairs

Dear Ms. Martin:

Please refer to your New Drug Application (NDA) dated January 13, 2011, received January 14, 2011, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Topiramate Extended Release Capsule, 25 mg, 50 mg, 100 mg, and 200 mg.

We also refer to your resubmission after refusal to file dated August 30, 2011, received September 09, 2011.

Additionally, we refer to your October 14, 2011, correspondence, received October 17, 2011, requesting review of your proposed proprietary name, Trokendi. We have completed our review of this proposed proprietary and have concluded that this name is unacceptable for the following reasons:

The proposed proprietary name, Trokendi, does not distinguish this extended-release product from currently marketed immediate release Topiramate products. This is problematic because Trokendi has overlapping strengths with the currently marketed Topamax and Topiramate products. Because Trokendi and the currently marketed Topiramate products are dosed with a different frequency of administration, an inadvertent substitution could lead to significant overdose or underdose of Topiramate.

Postmarketing surveillance of medication errors has identified wrong drug and wrong frequency errors which involve products with different release mechanisms that have overlapping product characteristics and fail to distinguish the proprietary names. Provider education and outreach strategies have failed to fully eliminate these types of errors from occurring. Ideally, we recommend avoiding overlaps in strength for drug products that have the same active ingredient but different formulations and frequencies of administration. However, if a strength modification is not feasible at this point in your product development, the nomenclature of this product might help to communicate the products extended-release properties.

In order to emphasize the difference between the proposed extended release Topiramate product and the currently marketed product, we recommend a modifier be appended to the proprietary name. The chosen

modifier should highlight the extended release properties of the proposed product in order to mitigate confusion between the currently marketed product and the proposed product and convey the different frequency of administration.

In order to initiate the review of an alternate proprietary name, submit a new complete request for proprietary name review. The review of an alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5058. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Jacqueline Ware at (301) 796-1160.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology

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/s/

CAROL A HOLQUIST
01/13/2012

Choy, Fannie

From: Tami Martin [tmartin@supernus.com]
Sent: Thursday, January 05, 2012 3:00 PM
To: Choy, Fannie
Cc: Ware, Jacqueline H
Subject: RE: FDA Information Request: re: NDA 201635

Hello Ms. Choy and Capt. Ware,

I apologize for the delay in responding to your query about the Direct Phase I clinical site where our clinical study 538P106-200 took place in late 2010. The company principal, Mr. Bonanaza, was finally reached by phone late during the holiday period. Although we had not been previously notified, he has confirmed what you mentioned in your email to us--- the company has closed due to bankruptcy.

Mr. Bonanza indicates that the documents for the study are in a storage facility, and he appears to be the party that could most easily arrange for access to the records. His contact information is below:

Bonanza Consulting Group, Inc.
Jason M Bonanza, MS
Clinical Research Consultant
5204 E. St. John Rd.
Scottsdale, AZ 85254
(b) (6)

The Principal Investigator, Dr Kyle Patrick, has the following phone number: (b) (6) We believe he practices either Family Medicine or Sports Medicine (or both?) in the Phoenix area.

Since the Direct Phase I clinical site is closed, when and if an inspection occurs, to whom will the FDA Form 482 be issued? We would also like to comment that we stand willing to assist in any reasonable way to obtain these records for your review. Please let us know if there is something further you would like us to do.

Tami Martin
VP, Regulatory Affairs
Supernus Pharmaceuticals, Inc.
301-838-2607
tmartin@supernus.com

From: Choy, Fannie [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Tuesday, December 20, 2011 6:30 PM
To: Tami Martin
Cc: Ware, Jacqueline H; Choy, Fannie

Subject: FDA Information Request: re: NDA 201635

Dear Tami,

Our team from the Office of Scientific Investigations has the following request related to the ongoing review of your pending NDA 201635 for Topiramate extended release capsule.

- The clinical site (Dedicated Phase I, Inc. Phoenix, AZ) for study 538P106-200 has declared bankruptcy. Please inform us whereabouts of the study data/records and the contact person so that the Agency could perform the inspection.

We ask that you please promptly respond to this request in order for the Agency to arrange site inspection.

If you have any questions, please do not hesitate to contact Jackie or me. Please acknowledge receipt of email.

Best regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4389
Silver Spring, MD 20993-0002
301-796-2899 phone
301-796-9842 fax
fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY
01/12/2012

Meeting Type: A
Meeting Category: Proprietary Name Review

Meeting Date: January 3, 2012
Meeting Location: FDA White Oak, Bldg 22, Rm 4266, Teleconference

Application: NDA 201635
Established Name: Topiramate Extended-Release Capsules
Applicant: Supernus Pharmacuticals

Meeting Chair: Carol Holquist, Director, DMEPA
Safety Evaluator: Julie Neshiewat, DMEPA
Meeting Recorder: Mark Liberatore, Project Manager, OSE

Applicant Attendees:
Tami T. Martin, RN, Esq., VP, Regulatory Affairs
Jocelyn McQueen, MS, Regulatory Affairs
Todd Horich, Ph.D, Director, Marketing
Pad Bhatt, Ph.D, VP, Pharmaceutical Sciences
Jack Khattar, President and CEO
Maria Pittaris, Asst. Director, Portfolio Management

Background:

Supernus Pharmaceuticals submitted the proposed proprietary name Trokendi, NDA 201635, for Topiramate Extended-release Capsules on October 14, 2011. If approved, this will be the first extended-release topiramate product on the market. The proposed strengths and dosing interval overlap with the currently marketed immediate release product. Additionally, the immediate release product is marketed in a sprinkle capsule. The established name of the product will indicate the product is immediate release; however, the proprietary name does not contain a modifier that indicates the extended-release properties of the product. Although there is no immediate release Trokendi on the market there is concern due to the product overlaps that this extended-release product may be confused as an immediate release product.

Meeting Objectives:

DMEPA requested this teleconference to discuss our concerns with the proposed proprietary name, Trokendi.

Discussion Points:

1) FDA asked for the rationale as to why a modifier, such as XR or XL, was not added to the proposed proprietary name of this extended release product? The Applicant indicated that since this NDA was an individual brand name, there was

no need to submit the name with a suffix modifier. Furthermore, the applicant had prior discussions with DNP regarding the established name of the drug containing "extended-release" or "controlled-release." The review division advised the applicant to use "extended-release."

2) FDA expressed their concerns that the proposed proprietary name Trokendi does not distinguish this extended-release product from the currently marketed immediate-release Topamax products. Trokendi has direct overlapping strengths with the currently marketed Topamax tablets (25 mg, 50 mg, 100 mg, and 200 mg) and Topamax sprinkle capsules (25 mg). We also note that Topamax can be initiated once daily, which overlaps with the frequency of administration of the proposed Trokendi extended-release product.

   DMEPA described postmarketing wrong drug and wrong frequency errors, which involve products with different release mechanisms that have overlapping product characteristics and fail to distinguish the proprietary names.

3) We acknowledged that we have not identified any safety concerns with the root name Trokendi. However, we did suggest that in order to emphasize the difference between the proposed extended-release topiramate product and the currently marketed Topamax immediate-release product, a modifier should be considered. FDA suggested to applicant to research suffix possibilities at www.ismp.org to determine the most common suffixes associated with once-daily dosing. FDA also suggested that the suffix should be consistent with other suffixes with a once-daily meaning.

Actions:

1) The Applicant agreed to withdraw the name "Trokendi," and resubmit the name with a suffix modifier as discussed. The applicant also indicated that they would submit the name with a primary and secondary choice of modifier.

2) FDA indicated to the applicant that if they choose a well established modifier which indicates once-daily dosing, a full 90 day review would be unlikely.

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/s/

MARK A LIBERATORE
01/09/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201635

FILING COMMUNICATION

Supernus Pharmaceuticals, Inc.
Attention: Tami Martin, RN, Esq.
Vice President, Regulatory Affairs
1550 East Gude Drive
Rockville, MD 20850

Dear Ms. Martin:

Please refer to your New Drug Application (NDA) dated August 30, 2011, received September 9, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Trokendi (topiramate extended-release) capsules 25 mg, 50 mg, 100 mg and 200 mg.

We also refer to your amendment dated October 14, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 9, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 11, 2012.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

LABELING

CONTENT OF LABELING

During our preliminary review of your submitted labeling, we have identified the following labeling format issues for your proposed package insert:

1. The **Highlights** (HL) of Prescribing Information should be limited in length to one-half page. We suggest that you either request a waiver for the requirement or submit revised labeling that meets the half page requirement.

2. The Product Title information is required in the HL. Product Title must be bolded and in the following order: the proprietary and established drug names, followed by the dosage form and route of administration.

3. Initial U.S. Approval information in HL should be the 4-digit year in which FDA initially approved of the new molecular entity.

4. Revision date should be the month/year of the application approval, and must be presented as "Revised: MM/YYYY" format.

CARTON AND CONTAINER LABELS

We acknowledge your August 30, 2011 submission of draft carton and container labeling, which is not representative of the labeling intended for market. Therefore, we request that you submit the carton and container labeling that is intended for market. The use of "Tradename" as a placeholder is appropriate at this time. Please keep in mind that the font for this placeholder should be representative of the font intended for use with the actual proprietary name.

We request that you resubmit labeling that addresses these issues by December 9, 2011. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

(b) (4)

If you have any questions, please contact Jacqueline Ware, PharmD., Senior Regulatory Project Manager, by phone or email at (301) 796-1160 or Jacqueline.Ware@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, MD.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

RUSSELL G KATZ
11/14/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201635

ACKNOWLEDGE RESUBMISSION AFTER REFUSE-TO-FILE

Supernus Pharmaceuticals, Inc.
Attention: Tami Martin, RN, Esq.
Vice President, Regulatory Affairs
1550 East Gude Drive
Rockville, MD. 20850

Dear Ms. Martin:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), in response to our March 14, 2011, refusal to file letter, for the following:

Name of Drug Product:	Topiramate Extended-Release Capsule 25 mg, 50 mg, 100 mg and 200 mg
Date of Application:	August 30, 2011
Date of Receipt:	September 9, 2011
Our Reference Number:	NDA 201635

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 8, 2011, in accordance with 21 CFR 314.101(a).

CONTENT OF LABELING

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

OTHER

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, please contact me by phone or email at (301) 796-1160 or Jacqueline.Ware@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jacqueline H. Ware, PharmD.
Senior Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

JACQUELINE H WARE
09/23/2011

Ware, Jacqueline H

From: Tami Martin [tmartin@supernus.com]
Sent: Thursday, June 09, 2011 2:53 PM
To: Ware, Jacqueline H
Subject: RE: Request for a second Type A meeting for NDA 201635

Dear Capt. Ware,

Acknowledging receipt of your message. Thank you so much for your reply.

FYI, we are now anticipating resubmission of NDA 201635 at the end of August. I know Martha Heimann was trying to determine when our resubmission was planned, so if you could also relay this information to her I would appreciate it. Recently, following our meeting on oxcarbazepine, I told her that our resubmission was likely due at the end of this month, and that is no longer the case.

Tami Martin
Supernus Pharmaceuticals, Inc.
301-838-2607
tmartin@supernus.com

From: Ware, Jacqueline H [mailto:Jacqueline.Ware@fda.hhs.gov]
Sent: Thursday, June 09, 2011 2:21 PM
To: Tami Martin
Cc: Ware, Jacqueline H
Subject: RE: Request for a second Type A meeting for NDA 201635

Dear Ms. Martin:

I have shared your meeting request with the Division's CMC and Biopharmaceutics review teams. They have considered your request as well as your specific question. They have determined that a meeting is not necessary. The issue raised by your question will be a matter of review once the NDA is resubmitted and filed. This specific issue will not affect the fileability of the resubmitted NDA.

Many thanks,
Jackie Ware

****

Jacqueline H. Ware, Pharm.D., RAC
Captain, United States Public Health Service
Senior Regulatory Project Manager
FDA/CDER/OND/ODEI/Division of Neurology Products
phone: 301-796-1160

From: Tami Martin [mailto:tmartin@supernus.com]

Sent: Friday, June 03, 2011 3:46 PM
To: Ware, Jacqueline H
Subject: RE: Request for a second Type A meeting for NDA 201635

Hello Capt. Ware,

FYI- The CD containing the formal request for a type A meeting is with FEDEX and should arrive at your offices on Monday AM.

Hope you have an enjoyable weekend!

Tami Martin
Supernus Pharmaceuticals, Inc.
301-838-2607
tmartin@supernus.com

From: Tami Martin
Sent: Wednesday, June 01, 2011 4:48 PM
To: 'Ware, Jacqueline H'
Subject: Request for a second Type A meeting for NDA 201635

NDA 201635
Supernus Pharmaceuticals, Inc.
Topiramate extended-release capsules

Hello Capt. Ware,

Please find attached a copy of a Type A meeting request we are sending in for NDA 201635. We have identified another question we would like to discuss prior to our planned resubmission. I hope that you will see that this is a rather specific discussion point, and that you will permit us to discuss this with you in a meeting setting.

We will be sending in the electronic version of this request on CD ASAP.

Please call me if you have any questions about this meeting request.

Tami Martin, RN, Esq.
Vice President, Regulatory Affairs
Supernus Pharmaceuticals, Inc.
Ph: 301-838-2607
mailto:tmartin@supernus.com

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/s/

JACQUELINE H WARE
07/28/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: August 31, 2012

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See attachment	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Tami Martin	Vice President, Regulatory Affairs
FIRM/ORGANIZATION	
Supernus Pharmaceuticals, Inc.	
SIGNATURE	**DATE** *(mm/dd/yyyy)*
Tami Martin, VP Regulatory Affairs	06/14/2011

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850

FORM FDA 3454 (10/09)

PSC Graphics (301) 443-1090 EF

Ware, Jacqueline H

From: Tami Martin [tmartin@supernus.com]
Sent: Tuesday, April 05, 2011 12:09 PM
To: Ware, Jacqueline H
Cc: Jocelyn Hietpas
Subject: RE: NDA 201635: Type A meeting regarding refusal to file
Importance: High

NDA 201635
Type A meeting scheduled for April 6, 2011

Hello Capt. Ware,

Our team has assembled and reviewed your preliminary comments. Again, thank you very much for providing them well in advance of the scheduled meeting.

At this time, we do not believe it is necessary to proceed with the April 6, 2011 meeting, so please remove it from your schedule. We may have one or two minor requests for clarification which we feel we will be able to state very specifically, and manage via an e mail inquiry. Assuming these clarification requests proceed on our end, I hope that you will be able to accommodate these requests in this manner.

We thank you again for your input; I'll be in touch with you about our plans for resubmission of the NDA.

Please let me know that you received this message.

Tami Martin, RN, Esq.
Supernus Pharmaceuticals, Inc.
301-838-2607
tmartin@supernus.com

From: Ware, Jacqueline H [mailto:Jacqueline.Ware@fda.hhs.gov]
Sent: Monday, April 04, 2011 2:34 PM
To: Tami Martin
Cc: Ware, Jacqueline H
Subject: RE: NDA 201635: Type A meeting regarding refusal to file

Dear Ms. Martin,
Attached please find the Division's responses to your meeting questions. Please share with your team and let me know if responses are adequate and if the April 6, 2011 meeting may be cancelled.

Many thanks,
Jackie Ware
****

Jacqueline H. Ware, Pharm.D., RAC
Captain, United States Public Health Service
Senior Regulatory Project Manager
FDA/CDER/OND/ODEI/Division of Neurology Products
phone: 301-796-1160

From: Tami Martin [mailto:tmartin@supernus.com]
Sent: Friday, March 25, 2011 10:58 AM
To: Ware, Jacqueline H
Cc: Jocelyn Hietpas
Subject: NDA 201635: Type A meeting regarding refusal to file

Hello Capt. Ware,

Per our phone conversation, please find attached a copy of the briefing package for the Type A meeting you have tentatively scheduled for April 6, 2011 regarding the Refusal to File letter Supernus received for NDA 201635. We are placing the esub discs in a FED EX package now for first delivery Monday, but I wanted to provide the BP body in this e mail –I'm hoping that this is of help in the interim. When we spoke, I know you preferred receipt today, but said very early Monday might also be OK. I thought FED EX for first delivery was still more fool proof than sending it by courier today (we have had mixed results using a courier service).

Could you tell me the time you reserved for the meeting on April 6th? When we spoke on the phone you were uncertain about the time. Although you'll find we are committing to present most of the items as requested, there are a couple of items that might benefit from discussion. Since we are local, my expectation is that we will come to the meeting just to resolve the few remaining points.

(b) (4)

Thank you.

Tami Martin
Supernus Pharmaceuticals, Inc.
301-838-2607
tmartin@supernus.com

From: Ware, Jacqueline H [mailto:Jacqueline.Ware@fda.hhs.gov]
Sent: Monday, March 14, 2011 1:05 PM
To: Tami Martin
Cc: Ware, Jacqueline H
Subject: FDA letter re: NDA 201635

Dear Ms. Martin:

Attached please find an electronic copy of the Agency's Refusal-to-File letter for NDA 201635/ (b) (4) (topiramate extended-release capsules) 25 mg, 50 mg, 100 mg, 200 mg. The original will be mailed.

Please confirm receipt and successful opening of the file.

Sincerely,
Jackie Ware

****

Jacqueline H. Ware, Pharm.D., RAC
Captain, United States Public Health Service
Senior Regulatory Project Manager

Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4346
Silver Spring, MD 20993-0002

phone: 301-796-1160
fax: 301-796-9842
email: jacqueline.ware@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JACQUELINE H H WARE
04/05/2011

Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Monday, April 04, 2011 2:34 PM
To: 'Tami Martin'
Cc: Ware, Jacqueline H
Subject: RE: NDA 201635: Type A meeting regarding refusal to file
Attachments: N201635 4611 mtg prelim comments v4411.pdf

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Many thanks,
Jackie Ware
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Jacqueline H. Ware, Pharm.D., RAC
Captain, United States Public Health Service
Senior Regulatory Project Manager
FDA/CDER/OND/ODEI/Division of Neurology Products
phone: 301-796-1160

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Sent: Friday, March 25, 2011 10:58 AM
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Cc: Jocelyn Hietpas
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Hello Capt. Ware,

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(b) (4)

Thank you.

Tami Martin
Supernus Pharmaceuticals, Inc.
301-838-2607
tmartin@supernus.com

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Sent: Monday, March 14, 2011 1:05 PM
To: Tami Martin
Cc: Ware, Jacqueline H
Subject: FDA letter re: NDA 201635

Dear Ms. Martin:

Attached please find an electronic copy of the Agency's Refusal-to-File letter for NDA 201635/ (b) (4) (topiramate extended-release capsules) 25 mg, 50 mg, 100 mg, 200 mg. The original will be mailed.

Please confirm receipt and successful opening of the file.

Sincerely,
Jackie Ware

****

Jacqueline H. Ware, Pharm.D., RAC
Captain, United States Public Health Service
Senior Regulatory Project Manager

Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4346
Silver Spring, MD 20993-0002

phone: 301-796-1160
fax: 301-796-9842
email: jacqueline.ware@fda.hhs.gov

PRELIMINARY MEETING COMMENTS

Meeting Category: **Discussion of Refusal-to-File issues**

Meeting Date and Time: April 6, 2011 2:15 pm EST
Meeting Location: FDA White Oak Campus, Building 22 Room: TBD

Application Number: NDA 201635
Product Name: Topiramate extended-release capsule
Indication: epilepsy
Sponsor/Applicant Name: Supernus Pharmaceuticals, Inc.

Introduction:
The following material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for April 6, 2011at 2:15 pm EST between the Supernus Pharmaceuticals and the Division of Neurology Products. This material is shared to promote a collaborative and successful discussion at the meeting. If there is anything in it that you do not understand or with which you do not agree, we very much want you to communicate such questions and disagreements. The minutes of the meeting will reflect the discussion that takes place during the meeting and are not expected to be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the Regulatory Project Manager), but this is advisable only if the issues involved are quite narrow. It is not our intent to have our preliminary responses serve as a substitute for the meeting. It is important to remember that some meetings, particularly milestone meetings, are valuable even if pre-meeting communications seem to have answered the principal questions. It is our experience that the discussion at meetings often raises important new issues. Please note that if there are any major changes to [your development plan/the purpose of the meeting/to the questions] (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting, but we will be glad to discuss them to the extent possible. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

1.0 BACKGROUND

The purpose of this meeting is to obtain Agency feedback on the acceptability for filing of Supernus' planned responses to Refuse-to-File issues outlined in the Agency's March 14, 2011 letter.

2.0 DISCUSSION

Note: FDA comments appear below in *italic* text.

2.1 General FDA Comments

FDA has reviewed the March 28, 2011 NDA submission that provides Supernus' responses to both the RTF issues and the Additional Comments and requests raised in the Agency's March 14, 2011 RTF letter.

It is FDA's expectation that Supernus will include all the items or rearrange all the items mentioned in Supernus' responses to RTF and Additional Comments and Requests in the appropriate sections in the NDA resubmission. In Section 2.2 (below) are the Agency's responses to specific questions raised by Supernus in the March 28, 2011 response document. In addition, in Section 2.3 (below) are additional comments from by FDA's biopharmaceutics group.

2.2 Specific FDA Responses to Questions

FDA has not included below full background for each issue/comment listed; please refer to Supernus' March 28, 2011 response document for full background and explanation regarding each question listed below.

2.2.1 Refusal To File Item #1

SUPERNUS RESPONSE TO REFUSAL TO FILE ITEM #1

Does the FDA agree with the proposed specifications for the known impurity (b) (4) and the residue on ignition?

Does the FDA agree with the proposed tests, specifications and method validations (Table 2) for topiramate drug substance?

FDA Preliminary Response:

This information will be reviewed in the NDA resubmission.

2.2.2 Refusal To File Item #2 a, b, and c

FDA Preliminary Response:

Supernus did not propose any specific questions in their responses to these issues. FDA acknowledges Supernus' intent to provide or relocate the information described to address this issue.

2.2.3 Refusal To File Item #3 a, b, and c

FDA Preliminary Response:
Supernus did not propose any specific questions in their responses to these issues. FDA acknowledges Supernus' intent to provide or relocate the information described to address this issue.

2.2.4 Refusal To File Item #4

SUPERNUS RESPONSE TO REFUSAL TO FILE ITEM 4
Can the FDA confirm that compendial procedures do not need to be validated and submitted?

Does the FDA agree with the proposed tests, specifications and method validations (Table 3, Table 4, Table 5 and Table 6) for the non-compendial excipients?

FDA Preliminary Response:
The compendial procedures do not need to be validated and submitted. However, Supernus needs to evaluate their suitability for their product. The proposed tests, specifications and method validations for the non-compendial excipients will be reviewed in the NDA resubmission.

2.2.5 Additional Comments and Requests – Comment #1

SUPERNUS RESPONSE TO ADDITIONAL COMMENT #1
Must Supernus provide batch analysis data for the research formulation batches used in the 538P101 and 538P102 clinical studies, although those early clinical studies will not be included in the NDA resubmission?

FDA Preliminary Response:
It is not necessary to submit batch analysis data for the research formulation batches in the 538P101 and 538P102 clinical studies.

2.2.6 Additional Comments and Requests – Comment #2

FDA Preliminary Response:
Supernus did not propose any specific questions in their responses to this issue. FDA acknowledges Supernus' intent to provide or relocate the information described to address this issue.

2.2.7 Additional Comments and Requests – Comment #3

FDA Preliminary Response:
Supernus did not propose any specific questions in their responses to this issue. FDA acknowledges Supernus' intent to provide or relocate the information described to address this issue.

2.2.8 Additional Comments and Requests – Comment #4, paragraph 3

SUPERNUS RESPONSE TO ADDITIONAL COMMENT #4, paragraph 3
Supernus requests further clarification from the FDA regarding testing all pellets and extended-release capsule strengths in various media (pH 1.0, pH 4.5, pH 6.8, pH 7.5, and water); is the data intended for comparison with any other profiles, or is it solely intended to provide information about *in vitro* drug release in various pH comparable to that of the GI tract?

FDA Preliminary Response:
At this stage, the testing should be carried out for characterization of drug release in an environment with ranging pH values comparable to that in the GI tract.

Supernus proposes to provide *in vitro* dissolution results (n=12) for the 50mg, 100mg, and 200mg extended-release capsules in various media (pH 1.1, pH 4.5, pH 6.8, pH 7.5, and water), since each of those strengths contains a unique combination of pellet types; (b) (4) and therefore Supernus proposes to exclude that strength from the evaluation in various media.

FDA Preliminary Response:
In vitro dissolution testing should be carried out for all strengths (including 25-mg) in all media listed above.

(b) (4)

FDA Preliminary Response:
This effort is baseline product characterization, so in vitro dissolution testing should be carried out for pellets and the capsules at all strengths as described above.

Supernus proposes [redacted (b) (4)].

Does FDA agree with these proposals?

FDA Preliminary Response:
No. The requested information is for basic product characterization and should be included in the NDA resubmission. The detailed dissolution method development report that integrates all considerations/aspects may be submitted during review (within 3-months after the NDA resubmission).

2.2.9 Additional Comments and Requests – Comment #4, paragraph 4

SUPERNUS RESPONSE TO ADDITIONAL COMMENT #4, paragraph 4
Topiramate drug substance is not stable under acidic conditions. Topiramate extended-release capsules contain [redacted (b) (4)] Marketed Topamax is an immediate release formulation which releases all topiramate content in a short period of time into the acidic environment of the stomach. The amount of topiramate released from the extended-release capsules into the gastric acidic environment is significantly less than that from Topamax of the same dose over the same period of time. Therefore, the impact of acidic environment on topiramate is expected to be less in the extended-release drug product than Topamax. Topiramate extended-release capsules have been tested in various clinical studies (refer to table within FDA's additional comment #5, paragraph 3), and the *in vivo* data has shown acceptable *in vivo* performance.

Because of the instability of topiramate drug substance *in vitro* under acidic conditions (pH 2), dissolution testing for the drug product was not carried out in low pH media. Topiramate extended-release capsules do not contain any delayed release components, and therefore dissolution testing in acid stage followed by buffer stage is not performed.

FDA Preliminary Response:
Based on the pH solubility profile for topiramate (from the Supernus report TR-10-032.00), topiramate is exposed to acidic media for at least 1 hr during solubility determination. Please provide information related to stability testing of topiramate under acidic conditions over a 2 hr period.

Suitability of the proposed dissolution method will be determined during review of dissolution information in all of the media listed above both for pellets and the ER capsules (all strengths). This information should be included in the resubmission.

2.2.10 Additional Comments and Requests – Comment #4, paragraph 5

SUPERNUS RESPONSE TO ADDITIONAL COMMENT #4, paragraph 5
The topiramate solubility study (TR-10-032.00) submitted in Module 3.2.P.2.1 of NDA 201635 was conducted with topiramate exposed to the acidic conditions for a relatively short timeframe; samples were promptly diluted in mobile phase (60:40 water:methanol) prior to analysis, thereby preventing any further degradation.

Data for stability of topiramate in various media (pH 1.1, pH 4.5, pH 6.8, pH 7.5, and water) will be included in the revised dissolution method development report, to be provided as detailed in the response to comment #4, paragraph 3.

FDA Preliminary Response:
As previously stated, please include these data in the resubmission. A detailed dissolution method development report that integrates all of the information may be submitted subsequently, during NDA review (within 3-months after the NDA resubmission).

As detailed in the response to comment #4, paragraph 4, topiramate extended-release capsules do not contain any delayed release components, and therefore dissolution testing in acid stage followed by buffer stage is not performed.

Based on demonstration of *in vitro* instability of topiramate drug substance at pH 1.1 as well as the absence of delayed release components in the drug product, Supernus proposes [redacted] (b) (4) Does the FDA agree?

FDA Preliminary Response:
No. The dissolution data and information requested for the pellets and the capsules are needed for primary product characterization and should be included in the resubmission.

Suitability of the proposed dissolution method for product release and the proposed dissolution specification will be determined after the dissolution method development report is submitted.

2.2.11 Additional Comments and Requests – Comment #5, paragraph 2

SUPERNUS RESPONSE TO ADDITIONAL COMMENT #5, paragraph 2
A revised dissolution method development report will be provided to include dissolution testing of the extended-release capsules in various media (pH 1.1, pH 4.5, pH 6.8, pH 7.5, and water), as detailed in the response to comment #4, paragraph 3.

FDA Preliminary Response:
A dissolution method report that integrates all the considerations may be submitted during the NDA review (within 3-months after the NDA resubmission) as long as the specified information and data requested above are provided in the resubmission.

2.2.12 Additional Comments and Requests – Comment #5, paragraph 2a

SUPERNUS RESPONSE TO ADDITIONAL COMMENT #5, item a
The pH solubility profile at 37ºC for topiramate across the typical gastro-intestinal pH range was provided in the NDA 201635 (TR-10-032.00) in Module 3.2.P.2.1, and will be provided in the NDA resubmission. The degradation rate of topiramate in various media (pH 1.1, pH 4.5, pH 6.8, pH 7.5, and water) will be included in the revised dissolution method development report, to be submitted as proposed in the response to comment #4, paragraph 3.

FDA Preliminary Response:
Please include the degradation information and data in the resubmission.

2.2.13 Additional Comments and Requests – Comment #5, item 2b

SUPERNUS RESPONSE TO ADDITIONAL COMMENT #5, item b
Dissolution testing of the extended-release capsules in various media (pH 1.1, pH 4.5, pH 6.8, pH 7.5, and water) will be provided as detailed in the response to comment #4, paragraph 3.

FDA Preliminary Response:
Please include the data and information for the pellets under the same conditions used for dissolution testing of the ER capsules.

2.2.14 Additional Comments and Requests – Comment #5, item 2c

SUPERNUS RESPONSE TO ADDITIONAL COMMENT #5, item c
The dissolution apparatus for topiramate extended-release capsules (USP apparatus 2) is commonly used for solid oral dosage forms, and was selected based on successful usage for other approved products (e.g. Adderall XR, Carbatrol, Equetro, Sanctura XR, and Oracea) developed by Supernus (when operating as Shire Laboratories, Inc.) with a similar drug product design (i.e. multiple pellet types in a capsule).

FDA Preliminary Response:
FDA's response: Suitability of the proposed dissolution method will be determined during review.

2.2.15 Additional Comments and Requests – Comment #5, item d

SUPERNUS RESPONSE TO ADDITIONAL COMMENT #5, item d
If overage of (b) (4) is added (b) (4) to achieve 100% label claim of drug substance and XR coating excipients in the pellet products, would the FDA agree that the theoretical target reported in NDA 201635 is applicable to the compensated process, and that the products made by the compensated process are equivalent to the non-compensated registration products?

FDA Preliminary Response:
We are not clear about the intent of the question. However, adding overage to the product to compensate for the demonstrated in-process loss with a full justification is usually acceptable. The total amount of overage must be included in the product composition in section 3.2.P.1.2.

Your proposal of adding overage (b) (4) *will be reviewed in the NDA resubmission.*

It is our concern that your registration batches are not representative of your commercial production batches since there was no overage added in your registration batches which you state were manufactured at commercial scale. It is important that a thorough understanding of the formulation and the manufacturing process is necessary prior to manufacturing of registration batches. Any changes made to the formulation or the manufacturing process after the registration batches are made may result in the re-manufacture of the registration batches using the final formulation and/or commercial manufacturing process.

If the FDA agrees with the above, does the FDA agree that dissolution testing of the registration batches serves as the testing of the proposed to-be-marketed product?

FDA Preliminary Response:

As stated previously, the issue about the differences between the registration batches and the proposed to-be-marketed product remains to be addressed. Dissolution testing of the registration batches submitted earlier will not serve as testing of the final proposed to-be-marketed product.

2.2.16 Additional Comments and Requests – Comment #5, paragraph 2

SUPERNUS RESPONSE TO ADDITIONAL COMMENT #5, paragraph 2
As indicated in the response to comment #1, Supernus will provide batch analysis data and relevant batch information from batches used in clinical studies in Module 3.2.P.5.4 in the NDA resubmission. (b) (4)

Is this approach acceptable to FDA?

FDA Preliminary Response:
No. Please see the previous response requesting dissolution testing for n=12 ER capsules.

2.2.17 Additional Comments and Requests – Comment #5, paragraph 3

SUPERNUS RESPONSE TO ADDITIONAL COMMENT #5, paragraph 3
A validation report for the current dissolution procedure and HPLC analysis was provided in Module 3.2.P.5.3 of NDA 201635, and will be included in the NDA resubmission. If any changes are made to the dissolution method, the appropriate validation documentation will be provided.

FDA Preliminary Response:
This will be acceptable.

2.2.18 Additional Comments and Requests – Comment #5, paragraph 4

SUPERNUS RESPONSE TO ADDITIONAL COMMENT #5, paragraph 4
Proposed dissolution specifications were provided in Module 3.2.P.5.1 and 3.2.P.5.6 of NDA 201635, and will be included in the NDA resubmission. If any changes are made to the dissolution method, the appropriate proposed specifications will be provided.

FDA Preliminary Response:
The proposed to-be-marketed product needs to be clearly identified. Please provide the respective proposed specifications in the resubmission.

2.2.19 Additional Comments and Requests – Comment #6

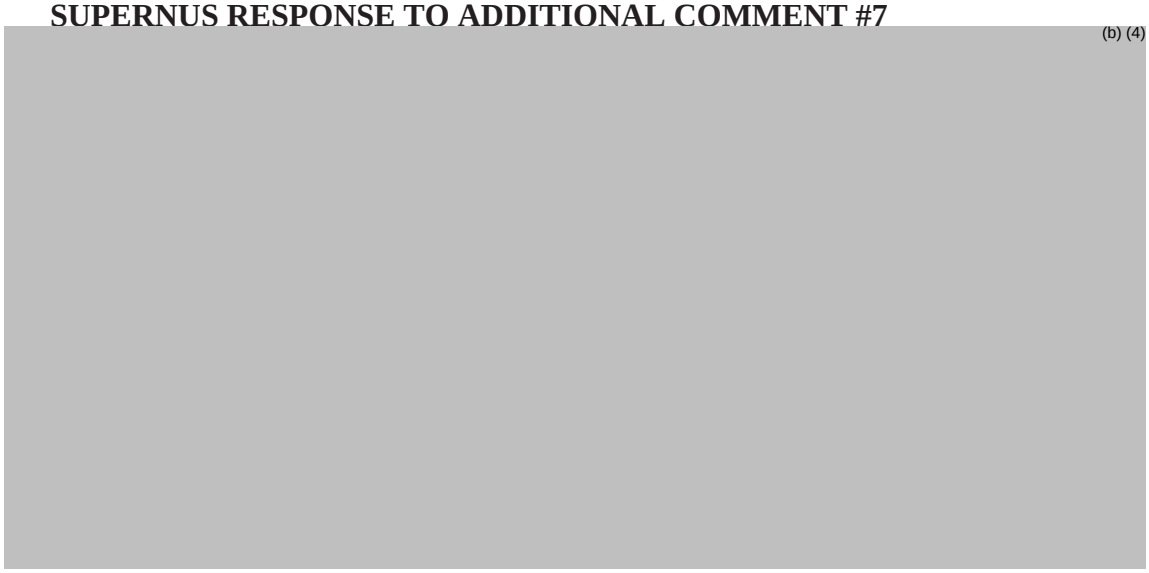
SUPERNUS RESPONSE TO ADDITIONAL COMMENT #6
Supernus does not plan to conduct this evaluation of pellet stability in pudding and yogurt, as we believe this additional evaluation is only necessary if the product labeling permitted sprinkle use of this product. Please comment on the company's position on this topic.

FDA Preliminary Response:
FDA has no comment on this issue at this time. The information will be reviewed in the NDA resubmission.

2.2.20 Additional Comments and Requests – Comment #7

SUPERNUS RESPONSE TO ADDITIONAL COMMENT #7

(b) (4)



(b) (4)

FDA Preliminary Response:
FDA has no comment on this issue at this time. The information will be reviewed in the NDA resubmission.

2.2.21 Additional Comments and Requests – Comment #1 in Clinical Pharmacology

SUPERNUS RESPONSE TO ADDITIONAL COMMENT #1 IN CLINICAL PHARMACOLOGY
Please confirm that the esubmissions group is willing to accept two define.pdf files in the same folder.

FDA Preliminary Response:
Please direct this question to CDER's Electronic Submissions group at esub@fda.hhs.gov.

2.2.22 Additional Comments and Requests – Comment #2a in Clinical Pharmacology

FDA Preliminary Response:
Supernus did not propose any specific questions in their responses to this issue. FDA acknowledges Supernus' intent to provide or relocate the information described to address this issue.

2.2.23 Additional Comments and Requests – Comment #2b in Clinical Pharmacology

SUPERNUS RESPONSE TO ADDITIONAL COMMENT #2B IN CLINICAL PHARMACOLOGY
Provision of these materials requires another clarification about the proper location of these materials in an esubmission. Based on discussions with our publisher, we plan to place all the output listings/control streams, etc in the following folder <m5\datasets\poppk\ analysis\programs> folder with additional user-defined sub-folders under programs as seen in the snapshot, below in order to keep the information organized. Is this approach acceptable?

FDA Preliminary Response:
Please direct this question to CDER's Electronic Submissions group at esub@fda.hhs.gov.

2.2.24 Additional Comments and Requests – Comment #3 in Clinical Pharmacology

SUPERNUS RESPONSE TO ADDITIONAL COMMENT #3
The protocol and Clinical Study Report submitted as part of the NDA refer to this meal as the "FDA high fat breakfast". Supernus is not planning any additional amendments/attachment or explanations to the CSR as part of the NDA resubmission. Please comment on this position.

FDA Preliminary Response:
FDA has no comment on this issue at this time. The information will be reviewed in the NDA resubmission.

2.2.25 Additional Comments and Requests – Comment concerning Proprietary Name

SUPERNUS RESPONSE TO ADDITIONAL COMMENT CONCERNING PROPRIETARY NAME
Supernus acknowledged this request and was planning to supply this in an amendment to NDA 201635 once the filing was accepted for review.

Please clarify, does "please submit a separate proprietary name review request to this NDA after you have submitted a response to this letter" mean that the proprietary name review request should be part of the NDA resubmission (if so, we propose placement in Module 1.12.4 Request for Comments and Advice), or should it be an amendment filed after the NDA resubmission has occurred?

According to the electronic communication received February 4, 2011, the PDUFA date for review of the proprietary name as submitted to IND 101,670 is April 19, 2011. Please clarify: May we still expect that the Division of Medication Errors and Prevention Analysis will respond to our proprietary name review request by April 19, 2011?

FDA Preliminary Response:
You should submit your proprietary name request amendment after the resubmission has occurred.

You may still expect DMEPA to respond by April 19, 2011.

2.3 Additional FDA Comments

FDA's biopharmaceutics group has provided the following summary comments. Included in each numbered point are: 1) item needed for review, 2) the purpose of the item, and 3) the submission timing for that item are also provided (the integrated dissolution method development report may be submitted during review if the main elements, as indicated, are included in the resubmission).

1. *Dissolution testing of pellets and extended-release capsule strengths(all) in various media (pH 1.0, pH 4.5, pH 6.8, pH 7.5, and water) as in guidance documents*
   Purpose: characterization of drug release from the pellets and the ER capsules (all strengths, including the 25-mg ER capsules) in an environment comparable to that in the GI tract.
   Timing: to be included in the resubmission.

2. *Solubility and stability testing (degradation) of topiramate in acidic pH over a 2 hr period.*
   Purpose: The originally submitted solubility data and comments related to stability of topiramate appear conflicting. The requested solubility and stability/degradation data and information will assist in interpretation of the results and ultimately, in determining suitability of the proposed dissolution method.
   Timing: to be included in the resubmission.

3. *A detailed and integrated dissolution method development report should include the above, in addition to all other data and information to support the proposed dissolution method and specification.*
   Purpose: Determination of suitability of the proposed dissolution method and dissolution/release specification

Timing: may be included during review (within 3-months after the NDA resubmission)

4. *In vitro dissolution data generated with the proposed dissolution method for the proposed to be-marketed drug product.*
   Purpose: in vitro characterization of the final proposed to-be-marketed product should be made using n=12 units(ER capsules) according to the final proposed dissolution method.
   Timing: These data should be submitted at the time of submission of the dissolution method development report.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JACQUELINE H H WARE
04/05/2011

Ware, Jacqueline H

To: Ware, Jacqueline H

Subject: FW: NDA 201635: Type A meeting regarding refusal to file

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From: Tami Martin [mailto:tmartin@supernus.com]
Sent: Friday, March 25, 2011 10:58 AM
To: Ware, Jacqueline H
Cc: Jocelyn Hietpas
Subject: NDA 201635: Type A meeting regarding refusal to file

Hello Capt. Ware,

Per our phone conversation, please find attached a copy of the briefing package for the Type A meeting you have tentatively scheduled for April 6, 2011 regarding the Refusal to File letter Supernus received for NDA 201635. We are placing the esub discs in a FED EX package now for first delivery Monday, but I wanted to provide the BP body in this e mail –I'm hoping that this is of help in the interim. When we spoke, I know you preferred receipt today, but said very early Monday might also be OK. I thought FED EX for first delivery was still more fool proof than sending it by courier today (we have had mixed results using a courier service).

Could you tell me the time you reserved for the meeting on April 6th? When we spoke on the phone you were uncertain about the time. Although you'll find we are committing to present most of the items as requested, there are a couple of items that might benefit from discussion. Since we are local, my expectation is that we will come to the meeting just to resolve the few remaining points.

(b) (4)

Thank you.

Tami Martin
Supernus Pharmaceuticals, Inc.
301-838-2607
tmartin@supernus.com

From: Ware, Jacqueline H [mailto:Jacqueline.Ware@fda.hhs.gov]
Sent: Monday, March 14, 2011 1:05 PM
To: Tami Martin
Cc: Ware, Jacqueline H
Subject: FDA letter re: NDA 201635

Dear Ms. Martin:

Attached please find an electronic copy of the Agency's Refusal-to-File letter for NDA 201635/ (b) (4) (topiramate extended-release capsules) 25 mg, 50 mg, 100 mg, 200 mg. The original will be mailed.

Please confirm receipt and successful opening of the file.

Sincerely,
Jackie Ware

****

Jacqueline H. Ware, Pharm.D., RAC
Captain, United States Public Health Service
Senior Regulatory Project Manager

Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4346
Silver Spring, MD 20993-0002

phone: 301-796-1160
fax: 301-796-9842
email: jacqueline.ware@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JACQUELINE H H WARE
04/05/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201635

REFUSAL TO FILE

Supernus Pharmaceuticals, Inc.
Attention: Tami T. Martin, RN, Esq.
Vice President, Regulatory Affairs
1550 East Gude Drive
Rockville, MD 20850

Dear Ms. Martin:

Please refer to your New Drug Application (NDA) submitted on January, 13, 2011, received on January 14, 2011, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (topiramate extended-release capsules) 25 mg, 50 mg, 100 mg, 200 mg.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the reasons described below.

CHEMISTRY, MANUFACTURING, AND CONTROLS

1) With regard to the drug substance specification [Module 3.2.S.4], you have not provided the analytical procedures to be used for acceptance testing. The specification should include adequate tests and analytical procedures to allow verification of each parameter reported on the manufacturer's certificate of analysis, regardless of whether the test is performed routinely on lot receipt or periodically for vendor requalification. Provide the test methods and supporting validation for all non compendial analytical procedures. Note that reference to established USP procedures is acceptable. Therefore, compendial procedures do not need to be submitted.

2) You have not provided the proposed composition, manufacturing process or controls for the commercial product. The following deficiencies are identified based on assessment of Module 3.2.P for the 200 mg capsule strength. Similar deficiencies were noted in the 3.2.P modules for the remaining strengths.

   a) Module 3.2.P.1 should contain the components and quantitative composition of the commercial formulation. Module 3.2.P.1 of your submission contains composition information for "Registration Scale Topiramate Extended-Release Capsules" accompanied by a statement that *"The commercial scale formulation ranges are being assessed. The final commercial formulation will be presented in the validation protocol and, once validated, will be used for future production batches."* Provide the composition for the to-be marketed product.

b) Module 3.2.P.3.2 should contain the proposed batch formula for commercial scale production. Module 3.2.P.3.2 of your submission contains batch formulas for registration scale batches of intermediate pellets and capsules and a statement that *"The commercial scale formulation ranges are being assessed. The final commercial formulation will be presented in the validation protocol and, once validated, will be used for future production batches."*

c) Per 21 CFR §314.50(d)(1)(ii)(*c*) the application should contain the proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a *commercial* lot of the drug product or a comparably detailed description of the production process for a representative batch of the drug product. Module 3.2.P.3.3 of your submission describes manufacture of registration scale batches rather than commercial manufacture. Provide the proposed commercial master batch record or a comparably detailed description for the commercial process.

3) Although the application is presented as an electronic Common Technical Document (eCTD) format submission; the organization of information within the Quality section does not conform to the CTD format. The following deficiencies are identified based on assessment of Module 3.2.P for the 200 mg capsule strength. Similar deficiencies were noted in the 3.2.P modules for the remaining strengths. Note that correction of these deficiencies will also require revision of related sections (e.g., Module 2.3 Quality Overall Summary and the Method Validation Package) that reference the cited sections.

a) Module 3.2.P.3.4 [Control of Critical Steps and Intermediates] references Module 3.2.P.5.6 [Justification of Specification] for specifications for intermediate immediate release and extended release pellets. Revise the application such that all information regarding specifications for intermediate pellets is located in Module 3.2.P.3.4.

b) Module 3.2.5.1 [Specification(s)] should contain the proposed regulatory specification for the commercial product. Instead it contains development and "provisional" specifications for intermediate pellets, bulk product, and packaged bottles and blisters for 'registration scale' batches. Revise the application such that the proposed commercial specifications, which are currently located in Module 3.2.5.6 [Justification of Specification], are located in Module 3.2.P.5.1.

c) The *in vitro* dissolution testing report, “Results Summary for In Vitro Dissolution Study for Topiramate Controlled Release Capsules (b) (4) 25mg and 200mg in the Presence of Alcohol”, which is currently in located in Module 4.2.2.1.1, should be moved to Module 3.2.P.2, “Pharmaceutical Development”.

4) Modules 3.2.P.4.1 and 3.2.P.4.2 for the noncompendial excipients (e.g., Docusate Sodium/ Sodium Benzoate, (b) (4) reference the manufacturer's test methods, which are not provided. Submit the analytical procedures to be used for acceptance testing and/or vendor qualification for all noncompendial excipients with appropriate validation data.

ADDITIONAL COMMENTS AND REQUESTS

We have the following additional comments and requests regarding your application that are not refuse to file issues. However, these comments should be addressed in your new submission.

CHEMISTRY, MANUFACTURING, AND CONTROLS

1) Module 3.2.P.5.4 should include batch analysis data for research and/or development batches used in clinical studies in addition to data for the registration batches.

2) In Module 3.2.P.8.1 you state that supportive stability batches are qualitatively and quantitatively similar to the registration batches and refer to section 3.2.P.2.2 for more information regarding composition. We are unable to locate any specific information regarding the composition of these batches (25 mg lot B08024A, 50 mg lot B08025A, 100 mg lot B08026A and 200 mg lot B08027A) in Module 3.2.P.2.2. Provide composition information for the supportive batches.

3) The post-approval stability commitment provided in Module 3.2.P.8.2 is inadequate. Revise the commitment to include placement of the first three commercial production batches per capsule strength on stability under long-term (25°C/60% R.H.), accelerated (40°C/75% R.H.), and, if appropriate, intermediate (30°C/65% R.H.) conditions.

4) The submission is poorly organized and the relevance of the submitted information with respect to the final proposed to be marketed product is not apparent.

   The dissolution method development report that you have provided has limited information and does not provide *in vitro* product characterization with respect to drug release (dissolution testing) from the topiramate ER capsules in conditions mimicking GI environment. Typically, dissolution testing, carried out in several media as in the guidance documents, also provide information about in vitro drug release in various pH comparable to the pH of the GI tract.

   Please provide *in vitro* dissolution test results of the pellets and the ER capsules (for all capsule strengths, n=12 units at each strength) in several media including pH 1.0, buffer (4.5, and 6.8), and in water, in addition to the proposed buffer (pH 7.5) dissolution media. (Reference: Guidance for Industry SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation, September 1997).

   You indicate that the product is not stable under acidic conditions (pH 2). However, you have not indicated how the integrity of the topiramate ER capsules and the pellets are going to be protected when they are in gastric pH. Typically, for delayed release products dissolution test is performed in 0.1 N HCl (acid stage) for 2 hrs followed by dissolution test in buffer (pH range 4.5 to 7.5). Please provide justification for omitting the acid stage testing.

   Furthermore, you have shown that topiramate solubility is approximately (b) (4) in physiologic pH (TR- TR-10-032.00). Based on this, the stated stability concerns are not

readily apparent. Please provide stability information for the pellets and the CR capsules in acidic pH followed by dissolution testing in buffer (pH range as above).

5) You have submitted a dissolution method development report (b) (4)

To support product characterization and an assessment of quality of the topiramate ER capsules, you need to provide a comprehensive dissolution method development report which should also include the above information (in Item#4) such that all relevant information is integrated and an assessment of the following can be made:

a) pH solubility profile for topiramate across the typical gastro-intestinal pH range (if topiramate stability is a concern, please provide the degradation profile.)

b) *in vitro* performance of the pellets and the ER capsules (as a dissolution profile) in several media [including pH 1.0, buffer (4.5, and 6.8)], and in water, in addition to the proposed buffer (pH 7.5) dissolution media.

c) Dissolution testing with different dissolution apparatus and under different conditions, leading to justification of the selected apparatus and conditions.

d) Dissolution testing should be carried out with a minimum of n=12 units at each strength of the final proposed to-be marketed product. If there is a difference in formulation composition between the batches studied in the submitted clinical studies (as summarized in the following table) and the proposed to-be marketed ER capsules, the differences should be provided in comparative tables.

The dissolution data submitted should be identified with batch and formulation numbers, batch sizes, manufacturing dates along with in vitro dissolution method, and test results (individual, n=12, and mean data). The dissolution data should be labeled with clinical study numbers, if the specific batch was used in the clinical studies.

Study #	25-mg CR capsule	50-mg CR capsule	100-mg CR capsule	200-mg CR capsule
SPN-538T-538P104	B08024B	B08025B	B08026B	B08027B
Protocol 538P105				B08027B
SPN-538T-538P104.5	B08024C	B08025C	B08026C	B08027C
SPN-538T- 538P103		B08025D	B08026D	B08027E
Protocol 538P106			B08026E B10001B	
TPMT-538P109			B10001CP	
SPN-538T- 538P106-50		B08025E B10024C		
SPN-538T - 538P106-200				B08027F B10002D

Depending on the final proposed optimized dissolution method for product quality testing, a validation report on dissolution procedure and HPLC Analysis of topiramate in pellets and capsules may be needed.

In addition, based on the final proposed dissolution method, please provide proposed dissolution specification for the pellets and the topiramate ER capsules.

6) You have tested administering capsule contents in applesauce in a clinical study (TPMT-538109) and need to assess in vitro product performance (integrity: stability and degradation profile, and release of topiramate from topiramate pellets after being kept in apple sauce).

In addition, for labeling purposes, stability of the pellets in other soft foods such as pudding, yogurt, etc. should be evaluated over a period not to exceed 2 hrs.

REQUIRED PEDIATRIC ASSESSMENTS

7) Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have not adequately addressed how you will fulfill this requirement. (b) (4) [redacted] Please note that PREA requires development of an age appropriate formulation.

Please revise and submit your pediatric development program to address all pediatric age groups (birth up to 17 years).

CLINICAL PHARMACOLOGY

1. Please provide the electronic datasets for PK parameters as SAS transport files (.XPT) for all studies.

2. Please submit the following datasets and codes/scripts for reviewers to recreate modeling and simulations:

   a. All datasets and the final analysis dataset used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

b. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

3. Please specify the content of high-fat food (i.e., standard FDA high fat food) for the food-effect study, or direct the reviewer to where the information located.

PROPRIETARY NAME

We remind you of the February 4, 2011 electronic communication from the Office of Surveillance and Epidemiology regarding the proprietary name review for this product. As stated in that communication, please submit a separate proprietary name review request to this NDA after you have submitted a response to this letter.

USER FEES

We will refund 75% of the total user fee submitted with the application.

PROCEDURAL

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

If you have any questions, call or email Jacqueline H. Ware, Senior Regulatory Project Manager, at (301) 796-1160 or Jacqueline.Ware@fda.hhs.gov.

Sincerely yours,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
03/14/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201635

NDA ACKNOWLEDGMENT

Supernus Pharmaceuticals, Inc.
Attention: Tami T. Martin, RN, Esq.
Vice President, Regulatory Affairs
1550 East Gude Drive
Rockville, MD 20850

Dear Ms. Martin:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: (b) (4) (topiramate extended-release capsules) 25 mg, 50 mg, 100 mg, 200 mg

Date of Application: January 13, 2011

Date of Receipt: January 14, 2011

Our Reference Number: NDA 201635

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 15, 2011, in accordance with 21 CFR 314.101(a).

CONTENT OF LABELING

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 201635** submitted on January 13, 2011, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please advise where in the application it is located.

OTHER

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, please call me at 301-796-1160 or email me at Jacqueline.Ware@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jacqueline H. Ware, PharmD
Senior Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JACQUELINE H H WARE
02/18/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: August 31, 2012

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Tami T. Martin	Vice President, Regulatory Affairs
FIRM/ORGANIZATION: Supernus Pharmaceuticals, Inc.	
SIGNATURE: Tami T. Martin	DATE *(mm/dd/yyyy)*: 11/01/2010

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850

FORM FDA 3454 (10/09)

PSC Graphics (301) 443-1090 EF